La Depressió en Pacients amb Neoplàsia Hematològica

UNIVERSITAT DE BARCELONA

DEPARTAMENT DE PSIQUIATRIA I PSICOBIOLOGIA CLÍNICA
UNITAT DE PSIQUIATRIA I PSICOLOGIA MÈDICA.
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La Depressió en Pacients amb Neoplàsia Hematològica

Tesi per a optar al Grau de Doctor en Medicina i Cirurgia

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DEDICATÒRIA

A n'Ot, el petit gran milhomes
A en Nil, el molt honorable
Als que poguessin arribar, per si de cas

A la Maria mare, dona, amant, companya, artista, de paciència desmesurada per suportar i recolzar en aquest llarg doctorat

A l'actualment invisible i molt personalment admirada i supraestimada Marissa
A en Jere i na Pilar, visibles, grans intel·lectuals, i més grans germans

Als meus pares, Lluís Maria i Maria Lluïsa, per concebre'm, sobrealimentar-me, educar-me fins on vaig entendre, per guiar-me quan no hi veia, per aconsellar-me quan hi veia, per no veure quan no hi era, per la paciència, pel gran amor, per la immensa generositat, al que tot els hi dec (inestimable hipoteca vital encara que molt agraïble, impagable a la fi).

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A tots moltes gràcies

ÍNDEX

Pròleg

Aquesta tesi doctoral està estructurada seguint la normativa per a la presentació de tesis doctorals com a compendi de publicacions.

Tot seguint aquesta normativa aportem sis articles originals que segueixen una mateixa línea d'investigació: aspectes psiquiàtrics (bàsicament els referents a la depressió) i de qualitat de vida en pacients amb neoplàsia hematològica trasplantats de progenitors hemopoètics. Aquests articles es presenten en l'apartat "Publicacions" d'aquesta tesi en la seva versió original en anglès. El fruit de la present investigació representen el treball realitzat durant un període de 10 anys en els Departaments de Psiquiatria i Hematologia Clínica de l'Hospital Clínic i Provincial de Barcelona. Un dels nostres objectius fou el d'aconseguir realitzar les publicacions de la tesi en literatura mèdica no específicament psiquiàtrica. Malgrat que en l'àmbit psiquiàtric es tingui clara la importància i impacte de la patologia psiquiàtrica en el pacient afectat d'altres patologies mèdiques, en l'àmbit oncològic hi ha una certa distància, desconeixença i confusió envers els aspectes psiquiàtrics associats al càncer. El nostre ha estat un intent d'acostar la psiquiatria a una ciència mèdica a cops poc humanitzada, on pot prevaldre més la bioquímica pròpia de la malaltia que una apropiada "química " amb el malalt de la malaltia.

Així mateix, els resultats d'aquesta tesi també han estat presentats en múltiples congressos nacionals i internacionals en el decurs dels darrers vuit anys, obtenint en sis ocasions premis en reconeixement al treball presentat:

- Accèssit "Jóvenes Investigadores en Psiquiatría" l'any 1997, concedit per la "Sociedad Española de Medicina Psicosomática".

- En tres ocasions "Premi al Millor Treball de Investigació" en els anys 1996, 2001 i 2004 concedits per la "Societat Catalana de Psiquiatria".

- "Premio Sistema Nervioso Central al Mejor Trabajo de Investigación en Psiquiatría de Enlace" l'any 2000, concedit per la "Sociedad Española de Psiquiatría".

- "Premio Ramón y Cajal de Psiquiatría de Enlace" al millor treball d'investigació publicat per un autor espanyol en literatura internacional en l'any 2003, concedit per la "Sociedad Española de Medicina Psicosomática".

Finalment, i després de la publicació del sisè article d'aquesta tesi on es fa esment a l'impacte negatiu de la depressió major en la mortalitat dels pacients amb càncer, s'aconseguí un impacte mediàtic considerable a nivell de la difusió de la notícia en diversos mitjans de comunicació (TV1 de Catalunya, L'Empordà, La Vanguardia, El Periódico, El País, El Mundo, La Razón, ABC, diverses ràdios estatals, nombroses webs nacionals i iberoamericanes). Així doncs, un augment en la fertilitat del treball realitzat es produeix a l'aconseguir arribar, esperant sensibilitzar, a l'opinió pública per a informar de la importància de la depressió major pel malalt i per la seva malaltia.

Articles publicats i factor d'impacte

Els sis articles que fonamenten aquesta tesi han estat publicats en literatura internacional, amb un **factor d'impacte (FI) acumulat de 35,887** segons l'ISI JCR del 2005:

1. Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C. Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation. *J Psychosom Res* 2004; 57: 201-211. (**FI: 2,052**).

2. Prieto JM, Atala J, Blanch J, Carreras E, Rovira M, Cirera E, Gastó C. Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation. *Bone Marrow Transplant* 2005; 35: 307-314. (**FI: 2,643**)

3. Prieto JM, Atala J, Blanch J, Carreras E, Rovira M, Cirera E, Gastó C. Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation. *Eur J Cancer* 2006; 42: 1749-1755. (**FI: 3,706**).

4. Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C. Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol* 2002; 20: 1907-1917. (**FI: 11,890**)

5. Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C. Stem cell transplantation: risk factors for psychiatric morbidity. *Eur J Cancer* 2006; 42: 514-520. (**FI: 3,706**)

6. Prieto JM, Atala J, Blanch J, Carreras E, Rovira M, Cirera E, Gastó C. Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation. *J Clin Oncol* 2005; 23: 6063-6071. (**FI: 11,890**)

1. INTRODUCCIÓ I UNITAT TEMÀTICA

1.1 CÀNCER I TRASTORN PSIQUIÀTRIC

Malgrat que en els darrers anys el pronòstic de moltes variants de càncer hagi millorat de forma significativa, el seu diagnòstic i tractament va sovint associat a una important càrrega d'estrès. El pacient s'ha d'enfrontar a una sensació d'incertesa envers el futur, sovint d'una por a la mort; interrupció o afectació clara dels seus plans o estil de vida, tant a nivell familiar com sòcio-laboral; sentiments d'aïllament, estigma i culpabilitat; i entre d'altres més, els efectes negatius a nivell corporal per la malaltia en si i pel intensiu tractament anticancerós (1-7).

Donada l'evidència d'un elevat impacte a nivell psicològic en el pacient amb càncer, l'estudi d'aquesta àrea s'està constituint com un important aspecte de l'oncologia clínica. En la gran majoria de pacients en els que es diagnostica una patologia psiquiàtrica els símptomes de depressió i ansietat en constitueixen l'element central (1-8).

En revisions d'estudis de depressió (2,3) o ansietat (4) realitzats en diverses poblacions de malalts oncològics s'indica que degut a limitacions en la metodologia de recerca la prevalença d'aquests trastorns és incert: segons aquests estudis la prevalença de depressió varia d'un 1% a un 53% i la d'ansietat entre un 1% i un 44%.

La patologia psiquiàtrica, bàsicament depressió i/o ansietat, quan s'associa a altres patologies mèdiques pot representar un impacte negatiu en diverses àrees: reducció de la qualitat de vida (6,9,10), de l'estat funcional (11) i del nivell d'energia (12-14); increment en la càrrega simptomàtica (2,15,16) i en la intensitat del dolor (2,4,5,17,18); disminució del compliment del tractament mèdic i/o pautes de salut (19-21); increment en les despeses d'atenció de la salut (22,23) i de la durada dels ingressos hospitalaris (24-28); així com també possiblement una reducció en el temps de supervivència (7,10,29-39).

Considerem que la fase d'hospitalització per a realitzar el trasplantament de progenitors hemopoètics representa el marc ideal per a un estudi molt detallat de l'estat psíquic dels pacients amb càncer hematològic. Com a fruit de la present investigació, s'han publicat un seguit de sis articles que fan referència a diversos aspectes de patologia psiquiàtrica i de qualitat de vida durant la fase específica d'hospitalització pel trasplantament.

1.2 TRASPLANTAMENT DE PROGENITORS HEMOPOÈTICS

El trasplantament de progenitors hemopoètics es considera com un procediment mèdic altament agressiu que suposa un gran nombre d'estressos tant a nivell físic com psíquic (40-45): la gravetat de la pròpia malaltia de base, els efectes secundaris severs relacionats amb la quimioteràpia intensiva i/o irradiació corporal total, l'ús de procediments mèdics invasius, les múltiples complicacions mèdiques (infeccions freqüents, hemorràgies, anèmia important…), la situació d'aïllament dins la càmera estèril, la fase d'espera de la recuperació hematològica, canvis a l'autoimatge i sens dubte el risc de mort associat al procediment en si mateix (0%-36% segons les mostres) (40).

Aquest tipus de trasplantament està avui en dia instaurant-se com una part més del tractament oncològic convencional. Actualment més de 580 centres a Europa estan portant a terme més de 21.000 trasplantaments per any (46). Malgrat que el trasplantament es capaç de guarir una varietat important de malalties, el procediment segueix encara associat amb una morbilitat i mortalitat significativa (40).

Els candidats a rebre el trasplantament de progenitors hemopoètics són els pacients amb malalties malignes o no malignes que no responen a tractament convencional o quan es suposa una manca de resposta. Les indicacions clàssiques del trasplantament són les leucèmies agudes, la leucèmia mieloide crònica, l'anèmia aplàsica i algunes malalties congènites (immunodeficiències). En els darrers anys, les indicacions s'han ampliat a d'altres malalties com els limfomes, la malaltia de Hodgkin, el mieloma múltiple i certs tumors sòlids (40,41).

Per la curació de determinades malalties de la sang o determinats càncers és precís eradicar totes les cèl·lules anormals existents (canceroses o malfuncionants) mitjançant l'administració de dosis elevades de quimioteràpia amb o sense radioteràpia (condicionament del trasplantament). Tot i així, aquest tractament elimina no només les cèl·lules anòmales sinó també les cèl·lules mare sanes de la medul·la òssia, situació incompatible amb la vida de l'individu. Per restaurar la funció després de la quimioteràpia s'administren al pacient cèl·lules mare capaces de regenerar una medul·la òssia sana. Aquest procediment rep el nom de trasplantament de medul·la òssia o de progenitors hemopoètics. Històricament la font de cèl·lules mare o progenitors hemopoètics ha estat la medul·la òssia, per això s'utilitza el terme de "trasplantament de medul·la òssia". Tot i així, en els últims anys, s'estan emprant altres fonts de cèl·lules mare diferents a la medul·la òssia (de sang perifèrica o de cordó umbilical), per la qual

cosa es prefereix el terme "trasplantament de progenitors hemopoètics" que inclou tots els tipus de trasplantaments (40,41).

El trasplantament es pot fer amb cèl·lules de donant (trasplantament al·logènic) o amb cèl·lules del propi malalt (trasplantament autogènic) prèviament extretes, tractades i tornades a injectar posteriorment. El trasplantament al·logènic ofereix moltes possibilitats de curació per a diverses malalties de la sang. Tot i així, és també un procediment complex que s'associa freqüentment a complicacions que poden comprometre la vida del pacient. El trasplantament autogènic no es tracta d'un veritable trasplantament ja que les cèl·lules mare procedeixen del propi pacient. Aquestes s'obtenen quan el pacient ha respost al tractament de la seva malaltia i prèviament al tractament de condicionament del trasplantament. Aquest és un procediment més senzill que el trasplantament al·logènic i amb menys complicacions, tot i que en determinades malalties la probabilitat de curació és inferior. D'altra banda, és l'únic tipus de trasplantament disponible per a aquells pacients que no disposen de donant compatible (40,41).

1.3 TRASPLANTAMENT DE PROGENITORS HEMOPOÈTICS I QUALITAT DE VIDA

En relació al progrés mèdic i al conseqüent augment en la supervivència de pacients oncològics, s'ha produït un progressiu reconeixement de la importància de l'estudi de l'adaptació psicosocial i qualitat de vida en pacients trasplantats (42,43,47). Avui en dia no es només la supervivència lliure de malaltia (quantitat de vida) un objectiu a considerar sinó que ho és també l'estat global del pacient (qualitat de vida).

La qualitat de vida és un concepte complex, amb variació segons els autors en relació a les diverses dimensions que hauria d'englobar. En base a una revisió de la literatura i amb un creixent consens es suggereix que aspectes mèdics, psicològics i socials serien les àrees bàsiques a considerar (48). La valoració de la qualitat de vida pressuposa una anàlisi més exhaustiva dels costs i beneficis associats al trasplantament de progenitors hemopoètics que el que realitzem només en base a mortalitat i morbilitat.

Encara que existeixen molts qüestionaris de qualitat de vida disponibles per a l'ús en pacients de càncer, no n'hi ha cap que de forma consensuada s'erigeixi com el més adequat o de referència (49). Fins avui cap mesura de qualitat de vida s'ha validat específicament per a l'ús en pacients adults hospitalitzats per a rebre el trasplantament de progenitors hemopoètics. Tanmateix, existeix una enquesta de catorze qüestions, amb propietats psicomètriques

demostrades, que es desenvolupà per a ser utilitzada en nens durant l'hospitalització per a realitzar el trasplantament (50) i tres altres enquestes de qualitat de vida (amb un nombre de qüestions oscil·lant de 30 a 60), amb propietats psicomètriques també establertes, que varen estar dissenyades per a ser utilitzades en pacients adults en l'etapa posterior al període d'hospitalització (51-53).

Així doncs, donada la manca d'instruments de qualitat de vida específics, en la primera publicació del nostre grup de recerca aportem dades en relació a les proves de validació d'una sèrie d'escales psicomètriques destinades a ésser utilitzades de forma específica durant la fase d'hospitalització del trasplantament. Donada la considerable càrrega tant física com psíquica, imposada en el pacient durant la fase del trasplantament (40-45), ens plantejarem dissenyar una sèrie d'instruments que foren breus i fàcils d'administrar. El nostre grup de recerca va concebre un grup de quatre escales per a ésser valorades pel propi pacient: una de les escales consta de vuit qüestions i mesura símptomes específics relacionats amb el trasplantament, dues escales d'un ítem cadascú mesuren estat psíquic global i estat físic global i una altre escala d'un ítem mesura el nivell de fatiga.

Malgrat la recerca en la qualitat de vida en el trasplantament de progenitors hemopoètics ha augmentat en els darrers anys, la majoria dels estudis han estat realitzats amb una mostra reduïda i/o amb un disseny retrospectiu o transversal (40,42,43). La gran majoria d'estudis s'han realitzat entre un i deu anys de forma posterior al trasplantament, estudiant-se els problemes associats amb l'adaptació a llarg termini, sense arribar a investigar-se l'impacte durant la fase d'hospitalització per a realitzar el trasplantament. Més recentment, uns pocs estudis longitudinals prospectius han inclòs una valoració prèvia al trasplantament i com a mínim una altre valoració durant la fase d'hospitalització (54-58). Inclús en aquests estudis prospectius la mostra de pacients fou limitada [n = 16 a 34 (54-57) i n = 97 (58)]. Les mesures de qualitat de vida objecte d'aquests estudis foren depressió (54-56,58), ansietat (54-56,58), funcionament neurocognitiu (54,55), fatiga (56), dolor (57) i una escala mesurant simptomatologia física (58). Entre els estudis prospectius que inclogueren com a mínim un seguiment de sis mesos posteriors al trasplantament (54,58), s'arribà a la conclusió que és durant el període d'hospitalització que el pacient patia els nivells més alts d'estrès físic (58) i psíquic (54,58).

Donades les limitacions metodològiques en la literatura actual, considerem com a valuosos aquells estudis longitudinals prospectius que mitjançant l'ús d'instruments psicomètrics validats valorin diversos aspectes de qualitat de vida durant la fase d'hospitalització

del trasplantament. Donat que són molt comunes les fluctuacions en la severitat i el curs dels símptomes físics i psíquics durant aquesta fase, els estudis que utilitzin mesures repetides en múltiples punts en el temps poden arribar a donar una visió més acurada de l'evolució de diverses variables de qualitat de vida durant aquest període tant estressant. El coneixement del funcionament emocional i físic des de la perspectiva del pacient, pot orientar en la presa de determinades decisions en relació al tractament a seguir (58,59), pot facilitar l'afrontament al procés de trasplantament (54,58-60) i ens pot servir per a dissenyar millores en les estratègies de prevenció i tractament (54,58-61). Alguns pacients poden utilitzar la informació sobre qualitat de vida en la seva decisió sobre l'acceptar com a opció terapèutica el trasplantament. Altres pacients poden incrementar el seu sentiment de seguretat i control en base a aquesta informació, amb unes expectatives més acurades facilitant el procés d'adaptació i afrontament. En adició, les mesures de qualitat de vida o d'estatus psicosocial durant la fase de trasplantament poden tenir un paper pronòstic en relació a l'adaptació posttrasplantament (58,60,62,63).

En general, els trasplantaments autòlegs es consideren com a més segurs i amb un impacte inferior a nivell de qualitat de vida respecte als trasplantament al·logènics, però en contrapartida estan associats a un major risc de recaiguda. En la gran majoria dels casos, existeix una indicació molt clara sobre el tipus de trasplantament a realitzar en funció de la malaltia del pacient, estadiatge i disponibilitat de donant. Uns pocs pacients (aquells amb leucèmia mielogènica aguda, limfoma no-Hodgkin, mieloma múltiple i leucèmia limfocítica crònica) poden considerar les dues opcions de trasplantament, autòleg o al·logènic, i poden beneficiar-se d'estudis comparatius de qualitat de vida durant la fase de trasplantament (59). En el segon estudi publicat pel nostre grup de recerca i utilitzant en part els instruments de qualitat de vida validats en la primera publicació, aportem informació detallada en relació al funcionament físic i psicològic del pacient durant la fase d'hospitalització, realitzant al mateix temps un estudi comparatiu entre els dos tipus de trasplantament. Per a la valoració del curs evolutiu setmanal de l'estat psíquic dels pacients, enlloc d'utilitzar el *Manual Diagnòstic i Estadístic dels Trastorns Mentals* (DSM-IV [64]) varem considerar més adient, de cares a obtindre una informació més precisa i detallada de símptomes depressius i d'ansietat, l'ús d'una escala molt utilitzada en la pràctica oncològica com és la Hospital Anxiety and Depression Scale (HADS [65]).

1.4 CÀNCER, FATIGA I DEPRESSIÓ

Dins la nostra investigació fem menció especial a la fatiga, un dels aspectes rellevants i alhora complexos, dins la qualitat de vida del

pacient amb càncer. La fatiga presenta una complexa interrelació amb el càncer i la depressió, podent-se manifestar com a símptoma d'ambdues entitats (3,7,12-14,64,66). Al mateix temps la fatiga també pot induir o agreujar la depressió, com a conseqüència de l'efecte advers en l'estat d'ànim i en la capacitat funcional del pacient. En afegiment, complicacions mèdiques o efectes secundaris de determinats tractaments poden causar al mateix temps fatiga i depressió (12-14,64,66). La fatiga és una de les manifestacions més freqüents en el càncer, indicant-se en diverses revisions d'estudis de fatiga associada al càncer unes prevalences que oscil·len entre un 25% a un 100% (12-14). La fatiga té un important efecte negatiu sobre la qualitat de vida del pacient, resultant en conseqüències adverses substancials a nivell físic, psicosocial, econòmic i laboral (56,66-68). Malgrat la recerca s'hagi incrementat en la darrera dècada, existeix poca informació en relació als factors clínics associats a la fatiga.

Algunes de les limitacions metodològiques en la recerca de la fatiga en el càncer inclourien: l'ús de qüestionaris no validats; l'estudi d'un nombre reduït de factors de risc; la manca d'atenció a la complexa interrelació entre fatiga, depressió i càncer; l'ús de mesures globals d'estrès que no mesuren per separat la depressió i l'ansietat; i la no aplicació de mètodes estadístics multivariants (12-14). De forma específica durant la fase de trasplantament, només un estudi ha aportat dades sobre factors clínics relacionats amb la fatiga (56). Aquest estudi presenta un mostra de pacients reduïda (n = 31) i una manca d'anàlisi mitjançant un mètode estadístic multivariant. En el tercer estudi publicat pel nostre grup, s'aporten dades en relació als factors de risc de fatiga durant el període del trasplantament, fent especialment esment a la relació entre depressió i fatiga.

1.5 TRASPLANTAMENT DE PROGENITORS HEMOPOÈTICS I TRASTORN PSIQUIÀTRIC

Les limitacions metodològiques de la literatura oncològica en relació a l'estudi del trastorn psiquiàtric i el seu impacte inclourien: l'ús de dissenys retrospectius o transversals; mostres esbiaixades; estudi d'un nombre limitat de factors de risc; inadequada avaluació de la complexa interrelació entre trastorn psiquiàtric i altres variables mèdiques referents a la malaltia de base, tractament citotòxic i a les freqüents complicacions mèdiques associades; manca de valoració mitjançant mètodes estadístics multivariants; i mostres reduïdes de pacients. En afegiment, la gran majoria dels estudis publicats han utilitzat qüestionaris autoadministrats en els que un resultat per sobre d'un determinat punt de tall es suggereix com a possible diagnòstic clínic, sense utilitzar de forma associada entrevistes clíniques

estructurades i/o criteris diagnòstics estandarditzats (1-5). Es considera com a mètode de referència per a una detecció acurada de trastorn psiquiàtric, l'ús d'entrevistes clíniques estructurades amb l'aplicació de criteris diagnòstics estandarditzats com el DSM-IV.

Només un estudi existent en la literatura ha investigat la prevalença i/o factors de risc multivariants de trastorn psiquiàtric durant la fase d'ingrés pel trasplantament de progenitors hemopoètics (8). Amb una mostra de 39 pacients trasplantats, Sasaki i cols. (8) varen diagnosticar un trastorn psiquiàtric segons criteris DSM-IV en 16 (41%) dels pacients trasplantats, essent els dos diagnòstics clínics més freqüents el de trastorn adaptatiu (23%) i el de trastorn de l'estat d'ànim (8%). Com a limitacions metodològiques d'aquest estudi senyalem l'escassa mostra de pacients i l'estudi de factors de risc d'un concepte de trastorn psiquiàtric global que comprenia un mostra molt heterogènia de patologies.

En aquells estudis realitzats durant la fase d'hospitalització del trasplantament i que només aporten els resultats en base a qüestionaris autoadministrats en els que un resultat per sobre d'un determinat punt de tall es suggereix com a possible diagnòstic clínic, les prevalences de depressió variaren d'un 20% a un 43% (54,60,69,70) i les d'ansietat d'un 20% a un 33% (54,60,71). Les limitacions en la metodologia d'aquests estudis inclourien la restricció de la valoració de morbilitat psiquiàtrica a només símptomes depressius i d'ansietat, només una valoració pretrasplantament associada a una (60,69-71) o dues valoracions més durant la fase d'hospitalització (54) i una mostra reduïda de pacients (n = 44-74 [54,69-71] i n = 120 [60]).

No existeix cap estudi publicat en la literatura que utilitzant un mètode estadístic multivariant hagi analitzat l'impacte de la morbilitat psiquiàtrica en el temps d'estada hospitalària per a realitzar el trasplantament. En el quart estudi publicat pel nostre grup de recerca, s'aporta informació en relació a la prevalença de la patologia psiquiàtrica i l'impacte d'aquesta en el temps d'estada hospitalària.

L'impacte negatiu que suposa la patologia psiquiàtrica quan s'associa a una altre malaltia mèdica (6,9-39), el patiment substancial a nivell emocional que representa pel pacient i el fet que els trastorns psiquiàtrics i en especial la depressió tendeixin a ésser interpretats com una reacció comprensible i inevitable davant el càncer (amb el conseqüent risc d'infradiagnòstic i infratractament [2,4,72,73]) posen de manifest la importància crítica d'identificar i tractar la patologia psiquiàtrica en els pacients trasplantats. El coneixement de la morbilitat psiquiàtrica en la fase de trasplantament (tipus de patologia, prevalença, curs evolutiu, factors de risc) pot contribuir a

una detecció precoç d'aquests trastorns i al disseny d'estratègies apropiades de prevenció i de tractament. En la cinquena publicació del nostre grup de recerca, s'aporta informació referent als factors de risc de patologia psiquiàtrica durant la fase de trasplantament.

1.6 DEPRESSIÓ I MORTALITAT EN EL CÀNCER

La depressió, definida per una gran varietat de mesures, ha estat associada de forma significativa amb un increment de la mortalitat en diferents patologies mèdiques (7,10,29-39). En les malalties cardiovasculars és on aquesta associació s'ha vist més freqüentment demostrada (29-32). Malgrat l'estudi de la influència de la depressió en la mortalitat de pacients amb càncer hagi donat resultats inconsistents, la gran majoria d'autors suggereixen una connexió (7,10,37-39). En una revisió recent de vint-i-quatre estudis publicats, en quinze d'ells es senyala una associació positiva entre la depressió i el progrés del càncer o mortalitat (7).

En relació a les limitacions en la metodologia de recerca dels diversos estudis de mortalitat cal ressaltar el fet que les mesures de depressió varen ser realitzades només en un determinat punt en el temps i amb una consideració inadequada de la complexa interrelació entre la depressió i altres predictors de mortalitat. Així mateix, la gran majoria dels estudis publicats varen definir la depressió només mitjançant l'ús de diferents qüestionaris autoadministrats (7,32). En contrast amb les mesures de depressió que venen definides per criteris diagnòstics estandarditzats, en les quals es tenen en compte l'evolució i intensitat de la clínica depressiva, les escales de depressió autoadministrades es troben limitades pel fet que només tenen en compte la clínica depressiva present durant la setmana anterior al moment de la valoració, amb el conseqüent risc d'una errònia classificació de persones com a deprimides com a resultat de circumstàncies vitals estressants o problemàtiques de salut presents en el moment de l'avaluació.

En relació als estudis de mortalitat posttrasplantament de progenitors hemopoètics, només en un estudi prospectiu amb més de 100 pacients s'examinà la relació entre depressió i mortalitat (10). Amb una mostra de 193 pacients, Loberizza i cols. (10) varen trobar que la depressió fou predictiva de mortalitat a curt termini (entre 6 i 12 mesos posttrasplantament), no evidenciant-se aquesta associació en la mortalitat a un més llarg termini (entre 13 i 42 mesos posttrasplantament). Dues limitacions metodològiques d'aquesta investigació són l'ús d'una mesura no validada de depressió (grup de símptomes depressius creat pels propis autors) i l'haver valorat la depressió només en una ocasió (en els sisè mes posterior al

trasplantament). En un estudi recent amb una mostra de 72 pacients, Akaho i cols. (74) varen trobar que una variable psicològica global (barreja de símptomes de depressió, ansietat, fatiga i confusió) valorada dues setmanes anteriors al trasplantament fou predictiva de mortalitat a curt termini (entre 3 i 8 mesos posttrasplantament) però no a un termini més llarg (entre 1 i 3 anys posttrasplantament). Els estudis oncològics que investiguen l'impacte de la depressió en la mortalitat poden presentar resultats contradictoris degut en part a la variabilitat en la llargada del període de seguiment (7). En la mesura que el temps de supervivència s'allarga, altres factors clínics poden aparèixer com associats a la mortalitat, així doncs dificultant el que es pugui evidenciar una relació entre depressió i mortalitat (7). En relació a la fase posterior al trasplantament de progenitors hemopoètics, la gran majoria de morts s'esdevenen dintre dels tres primers anys, essent la reducció més apreciable sobretot en els primers 12-24 mesos (75).

Donat que la depressió es una patologia que es manifesta de forma freqüent en pacients amb càncer (2,3,7,64), l'estudi del seu impacte en la mortalitat posttrasplantament adquireix una rellevància clínica significativa. En la sisena i darrera publicació del nostre grup de recerca, s'aporten dades referents a l'impacte de la depressió major en la mortalitat posterior al trasplantament de progenitors hemopoètics.

2. OBJECTIUS

En aquest apartat es descriuen els objectius específics de cadascuna de les sis publicacions que fonamenten la present tesi:

2.1 Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation

Analitzar les propietats psicomètriques dels quatre instruments de qualitat de vida (escales d'estat psíquic global, estat físic global, nivell d'energia i simptomatologia sistèmica) que l'equip de recerca va dissenyar per a ésser emprats durant la fase d'hospitalització per a realitzar el trasplantament de progenitors hemopoètics.

2.2 Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation

Descriure des del punt de vista del pacient el funcionament físic i psicològic durant la fase hospitalària de trasplantament. Els dos tipus de trasplantament, autòleg i al·logènic, es comparen en termes de variables psicològiques (depressió i ansietat segons l'escala HADS) i físiques (escales de estat físic global, nivell d'energia i simptomatologia sistèmica).

2.3 Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation

Identificar mitjançant anàlisi estadística multivariant els factors de risc associats a la fatiga durant la fase hospitalària de trasplantament. Estudiar de forma més específica la complexa interrelació entre fatiga i depressió.

2.4 Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation

Avaluar en base a criteris diagnòstics DSM-IV la morbilitat psiquiàtrica durant la fase hospitalària de trasplantament. Estimar l'impacte de la patologia psiquiàtrica (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) en la durada de l'estada hospitalària.

2.5 Stem cell transplantation: risk factors for psychiatric morbidity

Identificar mitjançant anàlisi estadística multivariant els factors de risc associats a la patologia psiquiàtrica (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) prevalent en el moment de l'admissió hospitalària o a la patologia psiquiàtrica incident durant el període de seguiment intrahospitalari.

2.6 Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation

Avaluar l'efecte de la depressió major diagnosticada durant la fase hospitalària de trasplantament, en la mortalitat en el primer, tercer i cinquè any posttrasplantament.

3. PACIENTS I MÈTODES

En el present apartat s'aporta un resum de les dades que considerem de rellevància. Per a una exposició més detallada, consulteu de forma específica l'apartat "Pacients i Mètodes" de cadascuna de les sis publicacions que fonamenten la present tesi.

3.1 POBLACIÓ D'ESTUDI

La mostra de població es constituí d'un seguit de pacients que de forma consecutiva varen ingressar a la Unitat de Trasplantament de Medul·la òssia de l'Hospital Clínic, entre les dades del 21 de juliol de 1994 i el 8 d'agost de 1997. Els criteris d'inclusió foren càncer hematològic, ésser més gran de 15 anys, no antecedents de trasplantament de progenitors hemopoètics i consentiment verbal informat.

De 253 pacients que reberen un trasplantament durant el període d'estudi, 235 compliren els criteris d'inclusió. Degut a dificultats d'agenda dels investigadors, 15 pacients no varen poder ésser entrevistats. Tots els pacients que foren informats de l'estudi acceptaren ésser entrevistats. Així doncs, la cohort final d'estudi inclogué un 93.6% de la població electiva (220/235).

3.2 PROCEDIMENT

La investigació actual ha tingut per objecte el període d'ingrés hospitalari per a realitzar el trasplantament de progenitors hemopoètics. Com a part del protocol de valoració pretrasplantament, l'hematòleg responsable del pacient primerament informava dels objectius de l'estudi en relació a la valoració de la qualitat de vida i aspectes psicosocials relacionats amb la fase de trasplantament.

En el moment de l'admissió a la Unitat de Trasplantament, el psiquiatre investigador donava informació detallada sobre el disseny, objectius i aplicabilitat de l'estudi. Els pacients foren valorats en una primera entrevista estructurada dins les primeres 48 hores de la seva admissió hospitalària (dies -9 a -4 depenent del tractament de condicionament, T1), i subseqüentment de forma setmanal des del dia del trasplantament (dia 0, T2) fins el moment de l'alta hospitalària o mort (dia +7, T3; dia +14, T4; dia +21, T5;…). En cada punt d'avaluació, l'hematòleg realitzava una valoració del pacient en l'escala d'estat funcional de Karnofsky (76). La primera entrevista tenia una durada d'uns 15-45 minuts i incloïa dades

sociodemogràfiques, antecedents psiquiàtrics personals, estat psiquiàtric actual i tres escales d'un ítem cadascuna valorant estat físic global, estat psíquic global i nivell d'energia. En aquestes tres darreres escales d'un ítem dissenyades pels investigadors, els pacients havien d'avaluar el seu estat físic i psíquic global experimentat en la darrera setmana en una escala numèrica de 0 a 10 i el nivell d'energia en una escala numèrica de 0 a 100. En les escales d'estat físic i psíquic global el 0 estava associat amb la descripció "molt pobre" i el 10 amb "excel·lent". En l'escala del nivell d'energia als pacients se'ls hi demanava que avaluessin el seu nivell d'energia global actual en relació al que seria el seu estat habitual de salut. Després d'aquesta primera entrevista el pacient completava un seguit de tres instruments autoadministrats: el Nottingham Health Profile (77) per a mesurar qualitat de vida; el Psychosocial Adjustment to Illness Scale (78) per a valorar adaptació psicosocial; i l'escala HADS per a valorar símptomes depressius i d'ansietat (65). Aquesta escala de depressió i ansietat s'ha utilitzat de forma extensa en la literatura per a la valoració psicològica dels pacients amb càncer (79,80).

En les entrevistes subseqüents setmanals, varem administrar un protocol estructurat breu que durava uns 5-15 minuts. Aquestes entrevistes comprenien la valoració de l'estat psiquiàtric actual, simptomatologia sistèmica relacionada amb el trasplantament (escala de 8 ítems dissenyat pels investigadors), estat físic global, estat psíquic global, nivell d'energia i l'escala HADS. De forma posterior a l'alta hospitalària i utilitzant un formulari estandarditzat, J.M.P recollia informació referent a diagnòstics mèdics, resultats de laboratori, signes vitals, tractament psicotròpic i altres dades clíniques pertinents requerides per a valorar l'escala Bearman de toxicitat secundària al règim de condicionament (81), així com també revisava les històries mèdiques i d'infermeria per recollir tota aquella informació escrita que fes referència a l'estat psicològic del pacient durant el seu ingrés.

Tres entrevistadors varen participar en aquest estudi: l'investigador principal era psiquiatre (J.M.P), els altres dos eren un resident de psiquiatria en el seu quart any (J.A) que va participar en els primers 11 mesos de l'estudi i un altre psiquiatre (J.B) que va participar en la resta de l'estudi. La informació psiquiàtrica obtinguda de les entrevistes amb el pacient fou complementada amb informació procedent de la família i del personal mèdic i d'infermeria. Els diagnòstics psiquiàtrics foren assignats en unes trobades realitzades cada dos mesos, en les quals s'arribava a un diagnòstic de consens per a cada pacient. No es varen realitzar estudis de fiabilitat entre investigadors.

La investigació actual presenta un disseny naturalístic. No es va realitzar cap intent per influenciar el tipus o quantitat de tractament

psiquiàtric ofert als pacients. L'atenció psiquiàtrica va consistir en teràpia psicofarmacològica i/o sessions psicoterapèutiques breus proporcionades pel psiquiatre investigador. La intervenció psiquiàtrica podia estar requerida a petició del propi hematòleg o per decisió del psiquiatre investigador d'acord amb l'hematòleg. El protocol clínic de recerca va estar revisat i aprovat pel Comitè Clínic de Recerca del Departament de Psiquiatria.

3.3 VALORACIÓ PSIQUIÀTRICA

L'entrevista psiquiàtrica seguia un format estructurat, basant-se els diagnòstics psiquiàtrics en criteris DSM-IV. El nostre propòsit fou el de realitzar una entrevista psiquiàtrica relativament breu, prenent especial atenció als trastorns psiquiàtrics més comuns en pacients amb càncer, com són els trastorns adaptatius, de l'estat d'ànim i d'ansietat (2-8,82)

Els criteris diagnòstics del DSM-IV per al diagnòstic d'episodi depressiu major i trastorn adaptatiu eren valorats en l'entrevista pel clínic com a absent/subllindar i present en relació a la darrera setmana. En relació als trastorns d'ansietat, varem utilitzar preguntes rellevants pel diagnòstic en relació al trastorn de pànic, trastorn d'ansietat generalitzada, fòbies i trastorn obsessiu-compulsiu, i en cas de troballes positives, totes els criteris específics foren valorats. Malgrat que varem investigar els antecedents de consum d'alcohol i tabac, no varem realitzar un qüestionament específic sobre criteris d'abús o dependència.

Determinats símptomes depressius com són l'hiporèxia i la fatiga poden ser un resultat directe del procés neoplàsic o del tractament citotòxic, representant un problema metodològic alhora de realitzar el diagnòstic de depressió en el pacient amb càncer (2,3,7,65,83). Dins el marc del nostre estudi, en el qual el pacient rep un tractament citotòxic molt agressiu, la gran majoria de pacients durant la fase d'hospitalització pel trasplantament experimenten hiporèxia i fatiga. El DSM-IV requereix un símptoma per a ésser comptat com a criteri diagnòstic en l'episodi depressiu major només si no es pensa que pugui ser degut al càncer en si mateix o com a conseqüència del tractament citotòxic. Donat que es precisen un total de cinc criteris d'un total d'una llista de nou, el DSM-IV presenta un risc d'infradiagnòstic en el pacient amb càncer en fase de tractament. En la investigació actual, per a diagnosticar l'episodi depressiu major varem utilitzar tant el DSM-IV com un model diagnòstic modificat del grup de Sloan-Kettering. Per a fins de recerca, aquest model modificat de diagnòstic es considera el millor d'un grup d'altres tres possibles models doncs incrementa l'especificitat del diagnòstic (83). Aquest

procediment diagnòstic assegura el grup depressiu el més homogeni possible, amb el menor nombre de variables de confusió, així doncs incrementant la significació estadística i clínica de les dades de la recerca (83). En aquest mètode diagnòstic modificat s'elimina l'hiporèxia i la fatiga de la llista dels nous criteris, i es requereix quatre dels set criteris restants per a realitzar el diagnòstic de depressió major. En el article on es presenten les dades referents a l'impacte de la depressió en la mortalitat posttrasplantament s'utilitzà el concepte de depressió menor. Amb coherència amb el mètode diagnòstic modificat del grup de Sloan-Kettering, es requerí de dos a tres símptomes dels set criteris possibles per al diagnòstic de depressió menor.

3.4 ANÀLISI ESTADÍSTICA

A ressaltar dins d'aquest apartat que en totes les publicacions de la present tesi s'han utilitzat tècniques d'anàlisi estadística multivariant per a controlar l'efecte de múltiples factors que podrien haver actuat com a variables de confusió.

4. PUBLICACIONS

La present tesi es presenta com a compendi dels sis articles que s'han publicat en la literatura internacional. A continuació presentem aquests sis treballs en la seva versió original en anglès tal com han estat publicats en les revistes corresponents:

4.1 Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation.
Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C.
J Psychosom Res 2004; 57: 201-211.

4.2 Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation.
Prieto JM, Atala J, Blanch J, Carreras E, Rovira M, Cirera E, Gastó C.
Bone Marrow Transplant 2005; 35: 307-314.

4.3 Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation.
Prieto JM, Atala J, Blanch J, Carreras E, Rovira M, Cirera E, Gastó C.
Eur J Cancer 2006; 42: 1749-1755.

4.4 Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation.
Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C.
J Clin Oncol 2002; 20: 1907-1917.

4.5 Stem cell transplantation: risk factors for psychiatric morbidity.
Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C.
Eur J Cancer 2006; 42: 514-520.

4.6 Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation.
Prieto JM, Atala J, Blanch J, Carreras E, Rovira M, Cirera E, Espinal A, Gastó C.
J Clin Oncol 2005; 23: 6063-6071.

4.1 Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation.

Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E, Gastó C. *J Psychosom Res* 2004; 57: 201-211.

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Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation

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Abstract

Objective: To test the psychometric properties of four patient-rated quality of life (QoL) instruments devised by the authors: thee single-item instruments measuring (1) overall physical status, (2) overall emotional status, and (3) energy level, and one eight-item instrument measuring systemic symptoms. **Method:** In a prospective inpatient study conducted from July 1994 to August 1997, 220 patients aged 16–65 years received hematopoietic stem cell transplantation (SCT) for hematologic cancer at a single institution. Patients were assessed at hospital admission and then on a weekly basis during hospitalization until discharge or death. **Results:** Internal consistency reliability and test–retest reliability of the tested scales were adequate. Convergent, divergent, criterion, and predictive validities as well as responsiveness to change of our scales were demonstrated by significant associations with their tested constructs. **Conclusion:** Our data indicate that the four QoL instruments are reliable and valid for use during hospitalization for SCT.

Keywords: Hematopoietic stem cell transplantation; Hospitalization; Quality of life; Reliability; Validity

Introduction

Hematopoietic stem cell transplantation (SCT) is rapidly becoming a part of conventional cancer treatment. Over 580 teams in Europe perform more than 21,000 stem cell transplants a year [1]. Patients with malignant or nonmalignant diseases who fail to be controlled by conventional means or when failure is expected are candidates for SCT [1,2].

Although research on quality of life (QoL) issues in the adult SCT population is constantly progressing, most of the published studies are small in size and retrospective or cross sectional. Moreover, many studies have been performed 1–10 years after SCT and have examined the problems associated with long-term adjustment but have not investigated the impact during hospitalization for SCT [3,4]. More recently, prospective longitudinal studies have measured QoL issues both before and at multiple points after hospitalization for SCT [5–18]. One of the limitations of these longitudinal studies is the small sample size; only two studies included more than 100 subjects in their analyses ($n = 130$ [13] and $n = 125$ [16]). A further limitation is that after the pre-SCT baseline assessment, there was no further observation until a few months post-SCT [5–14]; few studies have reported at least one [15,16] or more [17,18] evaluations during hospitalization for SCT. Because fluctuations in severity and course of physical and emotional symptoms during hospitalization for SCT are common, studies using repeated measures at multiple points in time may be give a more accurate reflection of QoL outcomes during this highly stressful period.

The few prospective longitudinal studies including at least one in-hospital evaluation and a minimum of 6 months of post-SCT follow-up [15–18] indicate that it is during the hospitalization period that individuals experience the highest levels of physical symptomatology [18] or psychological distress [15–18], as well as poorer outcomes on a range of

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QoL subscales [15]. Our finding that 44% of our 220 patients during hospitalization for SCT met criteria for a psychiatric disorder (mainly depressive, anxiety, and adjustment disorders) [19] reinforces the view that the hospitalization period is associated with a considerable emotional burden. In addition to the diagnosis of a life-threatening illness, patients hospitalized for SCT have to cope with numerous sources of stress such as invasive medical procedures, severe toxicity side-effects resulting from an intensive conditioning treatment, frequent medical complications, changes in body image, protective isolation, and the risk of mortality from the procedure itself [2–4,20–22].

Although many QoL questionnaires are available for use with cancer patients, there is no ''gold standard'' or ''best'' QoL measure [23]. To date, no QoL measure has been validated specifically for use in adult patients hospitalized for SCT. However, there is a 14-item QoL questionnaire with established psychometric properties that was developed for children during hospitalization for SCT [24] and three other QoL questionnaires with good psychometric properties that were constructed to be used with adult patients outside the hospitalization period [25–27]. McQuellon et al. [25] developed a 12-item bone marrow transplant subscale, which assesses specific SCT-related concerns. This subscale was not designed to be used alone but only as a complement to the general Functional Assessment of Cancer Therapy, which is a 35-item instrument widely used in clinical trials by a number of cooperative groups [28]. Psychometric testing was carried out at the time of hospital admission prior to the onset of side-effects of the conditioning treatment for SCT, at the time of hospital discharge, and at 100 days post-SCT. Serial assessments during the hospitalization period were not included [25]. This overall 47-item instrument represents a considerable burden for patients if serial measurements during hospitalization are performed. The other two existing validated questionnaires included 30 [26] and 60 items [27] and were designed specifically for use with SCT survivors during the posthospitalization period.

Given these gaps in the current literature, prospective longitudinal studies using validated instruments during hospitalization for SCT are necessary (1) to characterize the psychological and physical impact from the patient's perspective, (2) to provide additional information for making treatment decisions and for coping with the transplantation process, (3) to improve prevention and treatment strategies, and (4) to understand problems of long-term adjustment with the benefit of a baseline before SCT. As has been reported in several prospective longitudinal studies, patients with higher levels of psychological distress pre-SCT tended to experience higher levels of psychological distress in the long term [13,16,18]. In the same line, McQuellon et al. [15] reported that patients with a better performance status pre-SCT tended to report better QoL at 1 year post-SCT. Moreover, QoL data are now frequently used in clinical research as outcome measures in clinical trials [29,30] or as predictors of survival and response to treatment [31–34].

Due to the strenuous physical and psychological burden imposed on the patient [2–4,20–22], we sought to use brief and easy to administer QoL instruments. We devised one eight-item instrument measuring specific systemic symptoms related to the SCT setting, two global single-item indicators measuring overall physical status and overall emotional status, and one single-item instrument measuring energy level. All four measures were designed to be rated by the patient. The purpose of this paper is to test the psychometric properties of these four patient-rated QoL instruments during hospitalization for SCT. Because the post-SCT period is associated with a high risk of developing functional deficits and psychosocial sequelae as a result of cumulative impairments [3,4,20,22], our four instruments may also be used to assess the time course of these QoL outcomes after SCT. As the present cohort was also evaluated at 6, 12, 24, and 36 months after transplantation, in following reports we will present data on the psychometric properties of our devised instruments during that post-SCT period.

Method

Study population

Patients were consecutively recruited from the SCT Unit, Hospital Clinic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were hematologic malignancy, age at least 16, first SCT, and verbal informed consent. Of 253 patients who received an SCT, 235 met the eligibility criteria. We excluded from the study those patients that could not be interviewed at the baseline assessment ($n = 15$). All patients who were approached agreed to be interviewed. The final study cohort thus included 93.6% of the eligible population (220/235). Detailed information on the transplant regimens, graft-versus-host disease prophylaxis, patient care, and physician's psychiatric assessment have been published elsewhere [19].

Conditioning regimens, graft-versus-host disease prophylaxis, and patient care

A variety of conditioning regimens were used during the study period, chosen on the basis of transplant type and hematologic cancer. Eighty-five (93.4%) out of 91 allogeneic SCT patients received cyclophosphamide and total body irradiation unless contraindicated by prior irradiation, in which case they received busulfan/cyclophosphamide. Autologous SCT patients received cyclophosphamide/total body irradiation, melphalan/total body irradiation, carmustine/etoposide/cytarabine/cyclophosphamide, carmustine/etoposide/cytarabine/melphalan, or melphalan. For allogeneic SCT patients, graft-versus-host disease prophylaxis consisted of short-course methotrexate and cyclosporine with or without metilprednisolone, or T-cell depletion and cyclosporine with or without metilprednisolone.

All patients were assisted in laminar airflow rooms and received *Pneumocystis carinii*, viral, bacterial, and fungal prophylaxis according to institutional protocols. Discharge criteria, which did not change over the course of the study, included engraftment, adequate oral intake, and control of medical problems.

Psychiatric assessment

The psychiatric interview followed a structured format with psychiatric diagnoses being defined according to standardized diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [35], and rated by the psychiatrist. We tried to keep the psychiatric interview relatively short, focusing on mood, anxiety, and adjustment disorders known to be common in cancer patients [36,37]. A psychiatric diagnosis was considered present at any specific assessment point if the patient was diagnosed with a DSM-IV mood, anxiety, or adjustment disorder. Psychiatric information from the patient interviews was complemented with information from the family and medical and nursing staff. Psychiatric diagnoses were assigned at a diagnosis meeting held every 2 months, at which a consensus diagnosis was reached on each patient. No interrater reliability assessment was carried out.

Validated scales

Karnofsky Performance Status Scale (KPS)

Hematologists rated their patients in deciles from 0 to 100, with lower scores reflecting greater impairment in normal activity, work, and self-care [38].

Nottingham Health Profile

This 45-item self-administered questionnaire measures perceived health problems in six dimensions: physical mobility, energy, pain, sleep, social isolation, and emotional reactions. Higher scores indicate more health problems. The reliability and validity of this scale have been demonstrated elsewhere [39]. In our investigation, we used the validated Spanish version [40].

Psychosocial Adjustment to Illness Scale—self report

This 46-item self-administered questionnaire measures adjustment to illness in seven psychosocial areas: health care orientation, vocational environment, domestic environment, sexual relations, extended family relationships, social environment, and psychological distress. Higher scores reflect increasing degrees of maladjustment. The reliability and validity of the questionnaire have been established elsewhere [41]. In our study, an authorized Spanish translation was used.

Hospital Anxiety and Depression Scale

This self-administered scale was specially designed to screen for psychiatric morbidity in patients with physical illness. In our analysis, we used the 14-item total score as a measure of psychological distress. Higher scores indicate greater distress. This instrument has been extensively documented in patients with cancer and its reliability and validity have been examined in a variety of diagnostic groups [42,43]. In our study, an authorized Spanish translation was used.

Scales devised by the researchers

The research team that devised our four QoL instruments included two psychiatrists and three hematologists from the SCT unit who all worked with cancer patients and were involved in psychosocial research. As a complement to a multidimensional assessment of QoL performed at the time of hospital admission previous to initiating the intensive conditioning treatment, we developed brief and simple patient-rated QoL instruments to be used during weekly in-hospital evaluations. Those aspects of QoL that the research team considered as relevant to measure during hospitalization were symptom experience and global indicators of physical and emotional status. In our study, we paid specific attention to energy level because fatigue is one of the commonest symptoms in cancer patients and is associated with significant levels of morbidity and poor QoL [3,44]. Fatigue has been reported as one of the most troubling side-effects during the hospitalization period in SCT patients [45] and was the most frequently reported symptom in two cross-sectional studies at a mean of 44 [46] and 55 months [47] post-SCT. Patients were asked to verbally rate the following four devised instruments with reference to the past week.

Overall physical and emotional status scales

In those one-item instruments, patients were asked to rate their overall physical or emotional health according to a 0 to 10 numerical rating scale. The scales were anchored at 0 with the statement ''very poor'' and at 10 with the statement ''excellent.''

Energy Level Scale

In this one-item instrument, patients were asked to rate their overall energy loss in relation to what could be considered their healthy state. The energy loss was rated on a scale of 0 to 100, and the energy level was obtained by subtracting the energy loss from 100.

Systemic Symptom Scale

This scale was meant to include physical symptoms specifically related to the intensive conditioning treatment experienced during hospitalization for SCT. The symptom list was developed by three hematologists of the SCT unit and based on their clinical experience and after a review of the literature [21,22,48,49]. Gaston-Johansson et al. [49] found that the most frequent pain symptoms during hospitalization for SCT were odinia, abdominalgia, generalized

pain, and headache. Eight symptoms were selected as the most relevant to be included in our systemic symptom scale: vomiting, nausea, diarrhea, dry mouth, odinia, abdominalgia, headache, and other pain (assigned the highest single score if various sources of other pain were present). Each symptom was assigned a severity score of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, or 3 = severe). A total systemic symptom score was obtained by summing all individual items.

Other study variables

On the basis of prior research, patients were divided according to their disease risk status into low, intermediate, and high [50]. Current smoking was defined as smoking one or more cigarettes per day within 1 month of hospital admission (one patient stopped smoking 1 month preadmission, one at 2 weeks preadmission, and the rest at hospital admission) since the onset of abstinence symptoms can range from 2 days up to several weeks after quitting smoking [35]. Length of hospital stay was defined as the number of overnight stays from day of transplantation (Day 0) until hospital discharge [19].

Procedures

The present report focuses on hospitalization for SCT, the initial stage of a prospective analysis in which physical and psychosocial functioning was also comprehensively evaluated at 6, 12, 24, and 36 months after transplantation.

Three interviewers participated in the study; the main investigator was a psychiatrist (J.M.P), the two others were a fourth year psychiatric resident (J.A) who participated in the study for the first 11 months, and a psychiatrist (J.B) who participated in the rest of the study.

As part of the pretransplant assessment protocol, hematologists first informed patients about the planned study of QoL and psychosocial aspects related to SCT. On their admission to the transplantation unit, the research psychiatrist gave detailed information about the protocol design, objectives, and the applicability of the study. Patients were assessed in a baseline structured interview within 48 h of hospital admission (T1, Day −9 to Day −4, depending on the conditioning regimen) and subsequently on a weekly basis from day of transplant (T2, Day 0) until discharge or death (T3, Day +7; T4, Day +14; T5, Day +21...). In some cases, interviews were conducted within 48 h of the scheduled days, either because the patient's medical status precluded the interview or due to scheduling difficulties. Collection of data at those specified time points was essential in order to control for variation in the physical and psychological condition of patients and the effects of treatment. At hospital admission and subsequently on a weekly basis, a KPS score was obtained from the hematologist. The first interview at T1 took 15–45 min and included sociodemographic data, past psychiatric history, current psychiatric status, and patient ratings of overall physical status, overall emotional status, energy level, difficulty in accepting the hematologic illness, and motivation for receiving SCT. After the interview, patients were asked to complete three self-report instruments: the Nottingham Health Profile, the Psychosocial Adjustment to Illness Scale, and the Hospital Anxiety and Depression Scale. In the following weekly assessments, and due to the significant clinical morbidity and isolation experienced by patients during hospitalization, we administered a brief structured protocol that took 5–15 min to complete. Due to patient fatigue and concerns about preventing infection, questions in this structured protocol were read aloud and responses written down by the interviewer. The brief structured protocol comprised the psychiatric assessment performed by the interviewer and patient ratings on the overall physical status, overall emotional status, energy level, systemic symptom, and Hospital Anxiety and Depression Scales. The clinical research protocol was reviewed and approved by the Department of Psychiatry's Committee on Clinical Research.

Attrition and missing data

A total of 1064 out of 1129 possible observations (94.3%) were made: 220, 217, 214, 201, 99, 49, 28, 13,

Table 1
Selected sociodemographic and medical characteristics ($n = 220$)

	n	Values
Mean age, years (S.D.)	220	38.4 (13.1)
Male sex (%)	129	58.6
White (%)	218	99.1
Married or living with partner (%)	141	64.1
Median education, years (IQR)	220	11 (8–15)
Current smoking (%)	41	18.6
Hematological cancer diagnosis (%)		
Acute myelogenous leukemia	50	22.7
Acute lymphoblastic leukemia	29	13.2
Chronic myelogenous leukemia	34	15.5
Non-Hodgkin's lymphoma	46	20.9
Hodgkin's disease	19	8.6
Multiple myeloma	27	12.3
Other[a]	15	6.8
Disease risk status (%)		
Low	86	39.1
Intermediate	33	15.0
High	101	45.9
Median time since diagnosis, months (IQR)	220	13 (7–24.8)
Autologous SCT (%)[b]	129	58.6
Peripheral blood stem cells (%)[c]	159	72.3
Chemoradiotherapy (%)	156	70.9
In-hospital death (%)	12	5.5
Median length of stay for survivors, days (IQR)	208	20 (17–27)

IQR = interquartile range.

[a] Chronic lymphocytic leukemia ($n = 7$), myelodysplastic syndrome ($n = 5$), histiocytosis ($n = 1$), myeloproliferative syndrome ($n = 1$), and granulocytic sarcoma ($n = 1$).

[b] One syngeneic SCT was placed with the autologous SCT group.

[c] Two patients with a combination of peripheral blood and bone marrow were included in this group.

9, 8, 4, and 2 at weekly assessments from T1 to T12 (Day +70). Missing observations were due to compromised medical status ($n=44$) or due to scheduling difficulties ($n=21$). Attrition was mainly due to hospital discharge and in some cases due to death ($n=12$). Those 1064 observations were made on the overall physical status, overall emotional status, and KPS scales. For the systemic symptom scale, we had the same number of observations from T2 to T12 (this scale was not measured at T1). Due to patient fatigue, in a few cases complete assessment of all instruments could not be performed. The total number of evaluations decreased slightly for the psychiatric assessment, energy scale, and Hospital Anxiety and Depression Scale to 1062, 1062, and 1058, respectively.

For those questionnaires that were only administered at T1, we found that 11 and 8 patients did not complete the Psychosocial Adjustment to Illness Scale and Nottingham Health Profile, respectively. We did not explore the reasons for this noncompliance. Because of partially incomplete data on some subscales of these two questionnaires, additional patients were omitted from statistical analyses. The total number of completed subscales at T1 varied between 207 and 210.

Statistical analysis

Normally distributed variables are reported as mean and standard deviation. Skewed distributed variables are presented as median and interquartile range. Due to the skewness of the QoL data, the analysis was based on nonparametric methods. Differences in KPS scores between consecutive assessment points were evaluated with Wilcoxon signed-rank tests. Comparison of proportions of patients who were diagnosed a DSM-IV psychiatric disorder between consecutive assessment points was evaluated with McNemar's χ^2 test. Internal consistency was assessed by use of Cronbach's alpha. Spearman rank order correlations were used to analyze test–retest reliability, convergent validity, and divergent validity. Criterion validity and responsiveness were analyzed using Mann–Whitney U tests. Univariate and multivariate linear regressions were used to test predictive validity. For the multivariate models, a stepwise selection method was used to select significant variables. Colinearity was assessed using variance inflation factors with standard residuals-based diagnostic procedures being used to assess model assumptions and adequacy of the model fit. Performance of the model was assessed by the adjusted explained variance.

Patients with missing data on any scale were excluded from analyses. All reported P values are two tailed. P values were considered significant if they were less than .05. No adjustment of the alpha level for multiple tests was made. All statistical analyses were conducted with the SPSS version 10.0 software (SPSS, Chicago, IL).

Table 2
Reliability of the overall physical status, energy level, systemic symptom, and overall emotional status scales[a]

	Overall physical status scale	Energy level scale	Systemic symptom scale	Overall emotional status scale
Test–retest reliability[b]				
T2 and T3 ($n=214$)	–	–	–	.69
T5 and T6 ($n=49$)	.59	.82	.75	–
T6 and T7 ($n=28$)	.84	.90	.61	.83
T7 and T8 ($n=13$)	.85	.77	.80	.90
Internal consistency reliability				
T2 ($n=217$)	–	–	.59	–
T3 ($n=214$)	–	–	.61	–
T4 ($n=201$)	–	–	.69	–

T2 = Day 0, T3 = Day +7, T4 = Day +14, T5 = Day +21, T6 = Day +28, T7 = Day +35, T8 = Day +42, – = not applicable.

[a] Spearman's rho correlation and Cronbach's alpha were used to analyzed test-reliability and internal consistency, respectively.

[b] All tested correlations had a $P<.001$.

Table 3
Divergent and convergent validity of the overall physical status, energy level, and overall emotional status scales[a]

	Overall physical status scale	Energy level scale	Overall emotional status scale
Divergent validity[b]			
T1 health care orientation PAIS ($n=207$)	−.08	−.02	−.13
Convergent validity[c]			
T1 energy NHP ($n=210$)	−.33	−.41	–
T1 physical mobility NHP ($n=209$)	−.36	−.42	–
T1 emotional reaction NHP ($n=209$)	–	–	−.33
T1 psychological distress PAIS ($n=207$)	–	–	−.44
T1 HADS ($n=220$)	–	–	−.52
T2 HADS ($n=216$)	–	–	−.53
T3 HADS ($n=214$)	–	–	−.70
T4 HADS ($n=199$)	–	–	−.62

T1 = hospital admission, T2 = Day 0, T3 = Day +7, T4 = Day +14, NHP = Nottingham Health Profile, PAIS = Psychosocial Adjustment to Illness Scale, HADS = Hospital Anxiety and Depression Scale, – = not applicable.

[a] Data expressed in Spearman's rho correlations. Data at T1 were correlated with the overall physical and emotional status scales and with the energy level scale while data from T2 to T4 was only correlated with the overall emotional status scale.

[b] All tested correlations had a $P>.05$.

[c] All tested correlations had a $P<.001$.

Results

Patient characteristics

Selected sociodemographic and medical characteristics are displayed in Table 1. Due to scheduling difficulties, 15 patients could not be interviewed at the first assessment and

Table 4
Criterion validity of the overall physical status, energy level, and systemic symptom scales[a]

Grouping variables[b]	Overall physical status score[c]	Energy level score[c]	Systemic symptom score[d]
T1 KPS score			
50–90 ($n=97$)	7 (2–10)	70 (0–100)	–
100 ($n=123$)	8 (3–10)	100 (40–100)	–
P	<.001	<.001	
T2 KPS score			
40–60 ($n=50$)	3 (0–7)	30 (0–100)	9 (2–18)
70–80 ($n=167$)	6 (1–10)	50 (0–100)	8 (0–15)
P	<.001	<.001	.003
T3 KPS score			
30–60 ($n=81$)	4 (0–8)	40 (10–90)	9 (4–20)
70–80 ($n=133$)	5 (2–10)	50 (0–100)	8 (0–19)
P	<.001	<.001	<.001
T4 KPS score			
40–60 ($n=45$)	5 (1–9)	40 (20–90)	7 (0–18)
70–90 ($n=156$)	6 (0–10)	60 (20–100)	5 (0–17)
P	<.001	<.001	.001

T1 = hospital admission, T2 = Day 0, T3 = Day +7, T4 = Day +14, – = not applicable.

[a] Data expressed in medians (range). Analysis was based on Mann–Whitney U test.

[b] KPS variables were categorized as lowest quintile versus rest of patients. When we used the lowest quartile or tertile, we obtained the same significant results (data not shown).

[c] Lower scores denote more dysfunction.

[d] Lower scores denote less symptoms.

were excluded from the study. There were no differences in age, sex, ethnicity, or hematologic diagnosis between the 220 patients who participated in the study and the 15 excluded patients.

Internal consistency reliability

In order to limit the number of dropouts in the internal consistency reliability analysis and in other psychometric testing such as the convergent, divergent, and criterion validity analyses, we only used data from the first four assessment points. Internal consistency, used as an index of the extent to which a set of items on a scale measure the same characteristic, was assessed for the eight-item systemic symptom scale. Cronbach's alpha coefficients were .59 at T2, .61 at T3, and .69 at T4 (Table 2). In addition, we calculated how much increase in reliability occurred if any combination of one, two, or three items were deleted and we only found a maximum increase in Cronbach's alpha of .06 after deleting the ''headache'' and ''other pain'' items at T2.

Test–retest reliability

To assess test–retest reliability (i.e., the stability of scores over brief periods of time) of the overall physical status, energy level, and systemic symptom scales during the hospitalization period, we attempted to find the period with fewest changes in KPS. We compared the KPS scores between consecutive time points and found significant differences from T1 to T5 (all $P<.001$) and a tendency towards stabilization from T5 to T8 (no significant differences from T5 to T6 and from T7 to T8 with $P=.046$ from T6 to T7). Therefore, in order to calculate test–retest reliability for these three scales, we used the time periods from T5 to T8 so that the coefficients obtained would better reflect measurement error rather than actual changes in physical status. We decided arbitrarily not to study further time points because the number of patients was below 10. To assess test–retest reliability of the overall emotional status scale, we attempted to find the period with fewest changes in proportion of patients who were diagnosed a DSM-IV psychiatric disorder. Comparing consecutive time points from T1 to T8, we found no significant differences in proportions among T2 and T3, T6 and T7, and T7 and T8. We therefore used those three time periods to calculate test–retest reliability for the overall emotional status scale. Test–retest reliabilities are presented in Table 2, with correlation coefficients ranging from .59 to .90 (all $P<.001$).

Convergent and divergent validity

The convergent and divergent validity of our scales was tested as follows: their convergent validity by examining associations with related scales and their divergent validity via their associations with an unrelated scale (Table 3). All these related and unrelated scales had been validated previously. There were no reliable measures available for convergent or divergent validation of the systemic symptom scale. The instruments tested for convergent validity analyses were significantly correlated with their related scales as expected (all $P<.001$). Divergent validity was demonstrated by the nonsignificant associations between our tested instruments and the unrelated scale.

Table 5
Criterion validity of the overall emotional status scale[a]

Grouping variables	Overall emotional status score[b]
T1 psychiatric diagnosis	
No ($n=174$)	8 (2–10)
Yes ($n=46$)	6 (1–10)
T2 psychiatric diagnosis	
No ($n=139$)	8 (2–10)
Yes ($n=77$)	6 (0–10)
T3 psychiatric diagnosis	
No ($n=141$)	8 (2–10)
Yes ($n=73$)	5 (1–10)
T4 psychiatric diagnosis	
No ($n=139$)	8 (3–10)
Yes ($n=62$)	6 (0–9)

T1 = hospital admission, T2 = Day 0, T3 = Day +7, T4 = Day +14.

[a] Data expressed in medians (range). Analysis was based on Mann–Whitney U test (all $P<.001$).

[b] Lower scores denote more dysfunction.

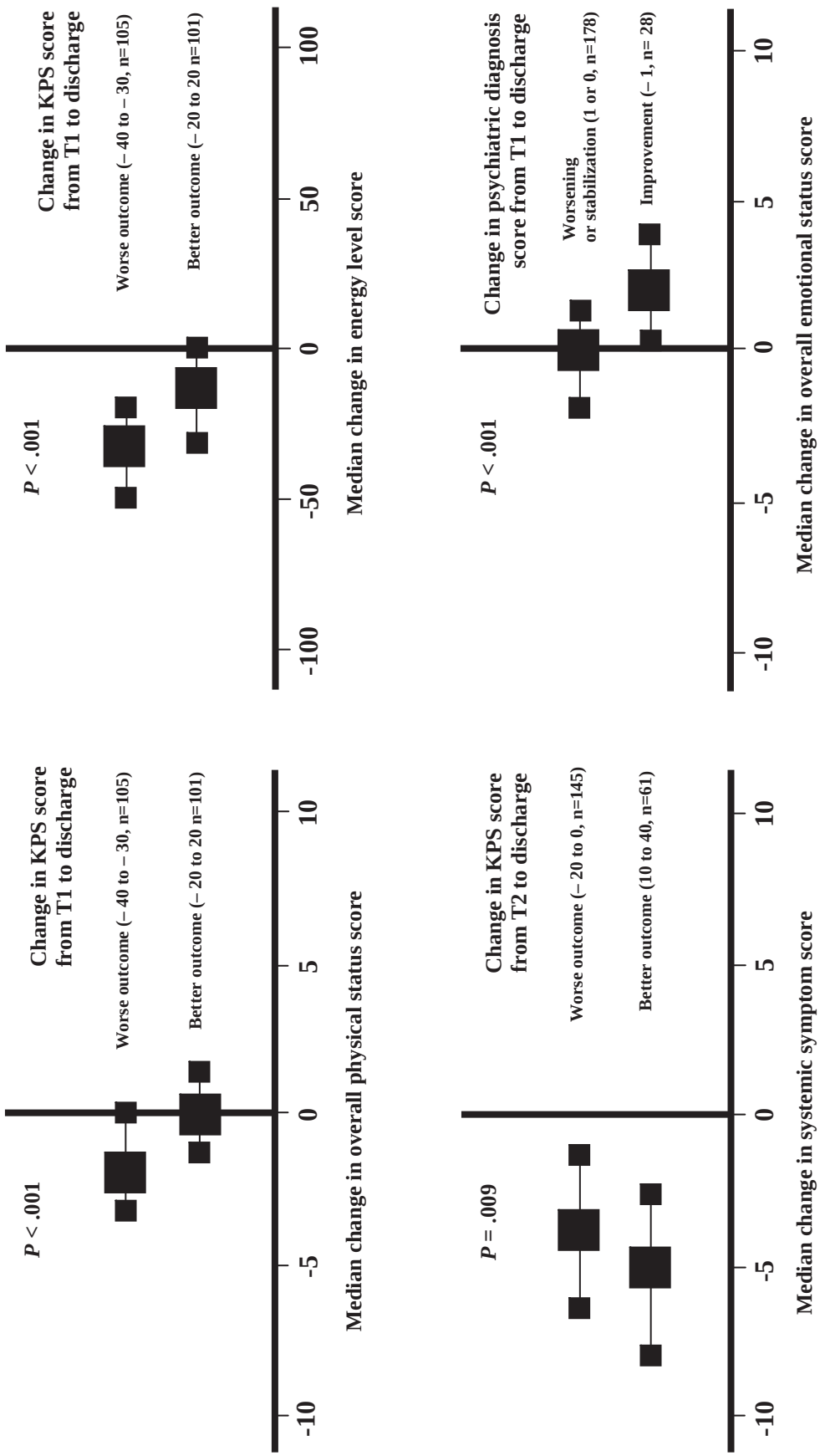

Fig. 1. Changes in KPS scores.

Criterion validity

To evaluate criterion validity, we used the method of known groups comparison to assess the ability of our scales to distinguish between subgroups of patients differing in clinical status (Tables 4 and 5). Our scales were found to be significantly related to their tested constructs at all assessment points. As expected, patients with poorer KPS scored significantly lower on the energy level and overall physical status scales and higher on the systemic symptom scale (Table 4). Again as expected, patients diagnosed with a psychiatric disorder scored significantly lower on the overall emotional status scale (Table 5).

Responsiveness or sensitivity to longitudinal change

As illustrated in Fig. 1, we assessed the responsiveness of systemic symptom, energy level, and overall physical status scales to changes in KPS from baseline (T2 for the systemic symptom scale and T1 for the rest of scales) to hospital discharge and the responsiveness of the overall emotional status scale to changes in psychiatric diagnosis (coded as 0 = no diagnosis and 1 = presence of diagnosis) from T1 to hospital discharge. Changes in scores in dependent and grouping variables were calculated by subtracting the score at hospital discharge from that at baseline, so that a negative change in KPS, energy level, overall physical and emotional status scores indicated worsening, and a negative change in systemic symptom and psychiatric diagnostic scores indicated improvement. The grouping variable change in KPS score was dichotomized, with patients in the lowest quintile being compared with the rest of patients. When we used the lowest quartile or tertile instead of using the lowest quintile, we obtained the same significant results (data not shown). The grouping variable change in psychiatric diagnosis score was also dichotomized: one category included 9 patients who had a change score = 1, with 169 patients who had a change score = 0, and the other category included those patients with a change score = −1. The association between change in our devised scale scores and the corresponding dichotomous grouping variable was calculated by using Mann–Whitney *U* tests. We excluded from the analysis those patients who died ($n = 12$) and those who had their last in-hospital interview at T1 or T2 ($n = 2$).

The responsiveness of our scales was demonstrated by significant associations in the expected direction with their tested constructs. The subgroup of patients whose KPS deteriorated the most from T1 to hospital discharge (−40 to −30; $n = 105$) reported a significantly worse outcome in overall physical status (median change, −2; $P < .001$) and energy level (median change, −30; $P < .001$) compared to the subgroup of patients with less decline in KPS (−20 to 20; $n = 101$; median change in overall physical status, 0; median change in energy level, −15). The subgroup of patients whose KPS declined or stabilized from T2 to discharge (−20 to 0; $n = 145$) reported a significantly worse outcome in systemic symptomatology (median change, −4; $P = .018$) compared to the subgroup of patients whose KPS improved (10–40; $n = 61$; median change, −5). The subgroup of patients whose psychiatric diagnosis score improved from T1 to discharge (−1; $n = 28$) reported a significantly better outcome in overall emotional status scores (median change, 2; $P < .001$) than patients whose psychiatric diagnostic score worsened or remained stable (0 or 1; $n = 178$; median change, 0; $P < .001$).

Predictive validity

Four separate regression analyses were conducted to determine whether baseline scores on our four devised scales could be predictive of their corresponding hospital discharge scores after controlling for other baseline risk factors. The common candidate explanatory variables in the univariate regression analysis for all four dependent variables included age, sex, education, living arrangements, current smoker, disease risk status, conditioning regimen, and type of SCT. The T1 psychiatric diagnosis (absence vs. presence) was added to predict the hospital discharge score on overall emotional status, and the T1 score on KPS [lowest quintile (50–90, $n = 97$) vs. rest of patients (100, $n = 123$)] was added to predict overall physical status, energy level, and systemic symptoms. When instead we used the lowest quartile or tertile, we obtained the same significant results (data not shown). Furthermore, the T1 score for each dependent variable was included in its corresponding regression model. All multivariate regression models were adjusted for sex and age. Those candidate variables with a marginal association ($P < .10$) or significant

Table 6
Baseline multivariate predictors of hospital discharge scores on the overall physical status, energy level, systemic symptom, and overall emotional status scales[a]

Dependent variables	Beta	*P*	Adjusted R^2
Overall physical status at discharge ($n = 206$)			
Education	−.212	.002	.06
T1 overall physical status	.203	.003	
Energy level at discharge ($n = 206$)			
T1 energy level	.288	< .001	.12
Age	−.142	.034	
Systemic symptom at discharge ($n = 206$)			
Age	.280	< .001	.10
T2 systemic symptom	.180	.010	
Overall emotional status at discharge ($n = 206$)			
T1 overall emotional status	.237	< .001	.09
Female	−.174	.011	
Education	−.165	.015	

T1 = hospital admission, T2 = Day 0.

[a] Only those significant ($P < .05$) multivariate predictors are listed. All multivariate regression models were adjusted for sex and age. We excluded from the analysis those patients who died ($n = 12$) and those who had their last in-hospital interview at T1 or T2 ($n = 2$). All significant multivariate predictors were treated as continuous variables except sex, which was coded as 0 = male and 1 = female.

association ($P<.05$) in univariate linear regression analysis (data not shown) were entered as a risk factors in multivariate regression models.

Table 6 shows the four multivariate regression models predicting hospital discharge scores on our four devised scales. In each of those four regression models, the baseline score that corresponded with the dependent variable was independently predictive of their hospital discharge score after controlling for other baseline risk factors. In addition, the following baseline variables were also found to be significantly predictive of poorer hospital discharge outcomes: higher educational level of poorer overall physical and emotional status, older age of lower energy level and higher systemic symptomatology, and female sex of poorer overall emotional status.

Discussion

To our knowledge, this is the largest study evaluating various aspects of physical and psychological function during hospitalization for SCT. We tested the reliability and validity of four patient-rated scales specifically devised by the authors for this study. The results demonstrated the instruments' reliability and validity.

All four instruments presented adequate test–retest reliability, with Spearman's correlation coefficients ranging from .59 to .90 (all $P<.001$). Although we tried to select the hospitalization period with fewest changes in clinical status, the lower coefficients may actually reflect changes in the patients' physical or psychological status. Since test–retest reliability is an index of temporal stability, higher correlation coefficients could be obtained if assessments were made in the posthospitalization period with patients with no treatment or associated complications.

Internal consistency reliability was acceptable for the systemic symptom scale, the Cronbach's alpha coefficients being .59 at T2, .61 at T3, and .69 at T4. There is no universally accepted cutoff for considering a Cronbach's alpha to be acceptable; some authors recommend that the internal consistency should be .65 or higher [51], while others consider .60 or higher as an acceptable level for research purposes [52]. However, in contrast to the standards used for research, a reliability of .80 may not be nearly high enough for making decisions about individuals [52]. When selection standards are quite rigorous, decisions about individuals may depend on small score differences (e.g., children with an intelligence quotient below 70 in a particular test are to be placed in special classes), and so it is difficult to accept any measurement error. A low alpha level suggests that some items either have very high variability or that the items are not all measuring the same thing. From a clinical point of view, the symptoms involved are not necessarily expected to occur at the same time. The aggregation of the items in our symptom scale is based on the need for clinically sensible summary scores and not necessarily on the need to make the scale more reliable. However, even without evidence of a high internal consistency for scales assessing symptoms or side-effects, one can still combine the items that make sense on clinical grounds [53].

With regard to convergent, divergent, and criterion validities as well as responsiveness to change, all patient-rated scales were significantly associated with their tested constructs, as we had expected. No reliable scales were available to assess the convergent or divergent validity of the systemic symptom scale. To minimize patient burden, we did not assess other validated scales that might have been used for psychometric testing.

Evidence of predictive validity was demonstrated in multivariate regression analysis by the ability of baseline scores on our four scales to significantly predict their corresponding hospital discharge scores. The finding that higher education attainment, a surrogate of higher socioeconomic status [54], was predictive of poorer patient-rated overall physical and emotional status at hospital discharge was contrary to expectations. Higher socioeconomic status has been associated with better health outcomes in many disease processes [54]. In a future report, we will present a detailed analysis of the complex interaction between education and poor patient ratings on health status measures. Although we do not know that the problems and priorities in our patient sample change along the post-SCT trajectory, in future articles we will study the ability of our measures to predict physical and psychological functioning at 6, 12, 24, and 36 months post-SCT as well as survival.

Although we did not measure interrater reliability on the psychiatric assessment performed by different interviewers, we sought to maximize the reliability of our psychiatric diagnoses by using standardized diagnostic criteria (DSM-IV), serial observations, multiple sources of information, and discussion in regular meetings between investigators.

After reviewing the literature on patient-rated psychological or physical functioning in adults patients during hospitalization for SCT, we found only one study that used a single-item instrument to rate a QOL outcome [55]. Schulz-Kindermann et al. used single-item numerical rating scales to measure anxious mood and depressed mood. Although these rating scales have previously been shown to be reliable and valid in pain research, no reliability or validity study was carried out in the setting of SCT. As regards symptom scales, two studies [18,56] used different patient-rated instruments to measure the impact of the SCT process on a symptom level. The symptom scales devised in those two studies were only tested for internal consistency reliability.

The eight-item systemic symptom scale was constructed from the physician's perspective. A limitation of our study was that SCT patients did not participate in the item generation phase of the systemic symptom scale. Further research is necessary to identify those physical symptoms that can be considered as more relevant from the patient's point of view. However, in the only published survey that assessed patient-rated complications of the intensive conditioning treatment

associated with SCT [45], odinia, nausea and vomiting, diarrhea, and fatigue were considered the most troubling side-effects. The fact that all these symptoms except fatigue are included in the systemic symptom scale adds more support to the scale's content validity. We did not include in our scale symptoms such as fatigue, anorexia, sleep disturbances, or concentration difficulties because we tried to avoid somatic symptoms that could also be an expression of a depressive or anxiety disorder [35–37,44]. Anorexia, sleep disturbances, and concentration difficulties were assessed in each weekly in-hospital assessment as a part of the psychiatric assessment. In our attempt to keep the scale brief, we may not have included other symptoms that might be considered as troubling from the patient's perspective. Other physical symptoms reported in those published studies using author-devised symptom scales [18,56] or a survey of patient-rated complications [45], and not included in our devised scale were difficulty swallowing, fever, skin changes, loss of mobility, and alterations in taste. Various global single-item instruments have demonstrated their psychometric properties in different cancer populations [57–60]. These instruments are written visual analog scales in which patients are required to place a mark on a line [58–60] or a long horizontal rectangle [57] anchored at both ends with words describing the minimal and maximal extremes of the dimension being measured. Due to patients' fatigue, concerns about preventing infection, and the fact that patients have to be in protective isolation during part of their hospital stay, we considered written visual analog scales as cumbersome to implement. As previously mentioned, the interviewer administered our devised scales verbally.

Multi-item tools covering all aspects of QoL and global single-item tools can be used as complementary approaches to QoL assessment. At the heart of the matter is the tradeoff between patient burden and the level of detail required. Administering QoL instruments in the SCT setting needs to be done with an acute awareness of the risk of patient overload. Completion of our four patient-rated instruments used during hospitalization required 1 min on average. The simplicity and ease of administration of these scales make them particularly attractive for hospitalization during SCT. In following reports, we will present data on the time course and associated multivariate risk factors of those outcomes as measured by our devised patient-rated scales.

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4.2 Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation.

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Quality of life

Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation

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Summary:

In this 3-year prospective inpatient study, 220 patients received stem-cell transplantation (SCT) for hematologic cancer at a single institution. The objective of the study is to provide data on patient-rated emotional (depression and anxiety) and physical (overall physical status, energy level, and systemic symptomatology) functioning during hospitalization for SCT and to compare whether these differ between autologous and allogeneic SCT. Patients were assessed at hospital admission (T1), day of SCT (T2), and 7 days (T3) and 14 days (T4) after SCT, yielding a total of 852 evaluations. For the overall sample, anxiety was highest at T1 and decreased afterwards; a marked worsening in physical health status variables corresponded with a sharp increase in depression from T1 to T3, and was followed by an improvement in physical health and a reduction of depression. Compared to allogeneic SCT, a better physical outcome for autologous SCT was demonstrated by the significant group effect for systemic symptomatology and by the significant group- × time interaction for overall physical status and energy level; there were no significant differences in depression or anxiety between SCT groups. These findings have implications for treatment decision making, coping with the transplantation process, and improving prevention and treatment strategies.

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Hematopoietic stem-cell transplantation (SCT) is becoming a part of conventional cancer treatment. Patients with malignant or nonmalignant diseases who fail to be controlled by conventional means or when failure is expected are candidates to receive SCT.[1,2] This procedure represents a highly aggressive and demanding medical therapy that has a profound impact on quality of life (QOL). It is associated with invasive medical procedures, severe toxicity side effects resulting from intensive conditioning treatment, frequent medical complications, changes in body image, protective isolation, and the risk of mortality from the procedure itself.[2,3]

Many QOL studies have been performed after SCT[3] and have examined the problems associated with long-term adjustment between 1 and 10 years post-intervention, but few have focused on its impact during hospitalization. The published reports of patient-rated emotional or physical functioning in adult SCT recipients during hospitalization for SCT have been characterized by methodological limitations such as small sample size and retrospective or cross-sectional designs. Among the prospective studies, only a few have included at least one preadmission or admission assessment plus more than one in-hospital evaluation.[4–8] Even in these prospective studies, the number of patients studied is frequently small ($n = 16$–34[4–7] and $n = 97$[8]). Outcome measures reported in these studies included depression,[4–6,8] anxiety,[4–6,8] uncertainty,[8] anger,[8] neurocognitive functioning,[4,5] fatigue,[6] nausea,[7] pain,[7] and a scale measuring physical symptomatology.[8] The prospective studies that also included at least 6 months of post-SCT follow-up[4,8] concluded that the hospitalization period was associated with the highest level of physical[8] and emotional[4,8] distress.

Given the methodological limitations in the current literature, longitudinal, prospective, empirical research that can be replicated is necessary.[8] Knowledge of the emotional and physical functioning during hospitalization for SCT from the patient's perspective can provide additional information that can help to make treatment decisions[8,9] and to cope with the transplantation process,[4,8–10] as well as to improve prevention and treatment strategies.[4,8–11] Some patients may use QOL data into their decision to undergo transplantation. Others may gain reassurance from this information, with more accurate expectations facilitating the coping process. In addition, QOL or psychosocial status measures can have a role in predicting post-SCT adjustment[8,10,12,13] or survival.[14]

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In general, autologous transplantations are thought to be safer and to have less impact on QOL than allogeneic procedures, but entail a greater risk of relapse. In most cases, a clear recommendation for either autologous of allogeneic SCT can be made after consideration of a patient's disease, stage, and donor availability. A few patients (those with acute myelogenous leukemia, non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia) may consider either autologous or allogeneic SCT and might benefit from comparative data.[9]

The purpose of the current descriptive paper was to provide prospective data during a 3-year period on patient-rated emotional and physical functioning during hospitalization for allogeneic and autologous SCT. These two SCT types were compared on emotional (depression and anxiety) and physical (overall physical status, energy level, and systemic symptomatology) health status variables that were evaluated at hospital admission and three consecutive weekly assessments during in-hospital follow-up.

Patients and methods

Study population

Patients were consecutively recruited from the SCT Unit, Hospital Clínic, Barcelona, between July 21, 1994 and August 8, 1997. Inclusion criteria were hematological malignancy, at least 16 years of age, patient's first SCT, and verbal informed consent. Of 253 patients who received an SCT, 235 met the eligibility criteria. Owing to scheduling difficulties, 15 patients could not be interviewed at the first assessment and were excluded from the study. All patients who were approached agreed to be interviewed. Thus, the final study cohort included 93.6% of the eligible population (220/235). There were no differences in age, sex, ethnicity, hematological diagnosis, or disease risk status between the 220 patients who participated in the study and the 15 who were excluded ($P > 0.20$).

Instruments

As this article's focus is on emotional and physical functioning throughout the hospitalization period, detailed description and results corresponding to other instruments only measured at hospital admission will be reported elsewhere. Some data were collected using instruments constructed specifically for this study because standardized assessment tools designed for our population were not available. The research team developed three brief and simple patient-rated QOL instruments to be used during weekly in-hospital evaluations: the overall physical status scale, energy level scale, and systemic symptom scale. In a previous report,[15] we demonstrated that these three instruments were reliable and valid for use during hospitalization for SCT. Internal consistency reliability was calculated for the only scale with more than one item (systemic symptom scale), with Cronbach's alpha coefficients reaching an acceptable level for research purposes[16] (0.59 at T2, 0.61 at T3, and 0.69 at T4). Test–retest reliabilities for the three scales were adequate, with correlation coefficients ranging from 0.59 to 0.90 (all $P < 0.001$). Convergent, criterion, and predictive validities, as well as responsiveness to change of the three scales were demonstrated by significant associations with the constructs tested (all $P < 0.019$). Divergent validity was demonstrated by the nonsignificant associations between our tested instruments and an unrelated scale (all $P > 0.05$).

Overall physical status scale. In this one-item instrument, patients were asked to verbally rate their overall physical health during the past week according to a 0–10 numerical rating scale. The scale was anchored at 0 with the statement 'very poor' and at 10 with the statement 'excellent'.

Energy level scale. In this one-item instrument, patients were asked to verbally rate their overall energy loss during the past week in comparison to what could be considered their healthy state. The energy loss was rated on a scale of 0–100, and the energy level was obtained by subtracting the energy loss from 100.

Systemic symptom scale. Patients were asked to verbally rate this eight-item scale inquiring about symptoms specifically related to the intensive conditioning treatment during the past week. The symptom list was developed by three hematologists of the SCT unit and based on their clinical experience and after a review of the literature.[7,17,18] Eight symptoms were selected as the most relevant to be included in our systemic symptom scale: vomiting, nausea, diarrhea, dry mouth, odinia, abdominalgia, headache, and other pain (assigned the highest single score if various sources of other pain were present). Each symptom was assigned a severity score of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, or 3 = severe). A total systemic symptom score was obtained by summing all individual items.

Hospital Anxiety and Depression Scale (HADS). This is a self-rating scale specially designed to screen for psychiatric morbidity in patients with medical illness. Somatic depressive or anxiety items that can be affected by illness or treatment side effects (eg weight loss and fatigue) have been removed to ensure more accurate assessment of this population. It contains two seven-item scales: one for depression and one for anxiety both with a score range of 0–21, with higher scores indicating greater distress. This questionnaire has been extensively documented in patients with cancer and its reliability and validity have been examined in a variety of diagnostic groups.[19,20,21] In our study, an authorized Spanish translation was used. Internal consistency, reliability, and correlation analysis for the HADS subscales was calculated at four time points from T1 to T4. The mean Cronbach's alphas were 0.88 (range 0.86–0.90) for the depression subscale and 0.84 (range 0.81–0.86) for the anxiety subscale. The mean Spearman's rank order correlation between the depression and anxiety subscales was 0.47 (range 0.37–0.55).

Study procedures

Detailed information on patient characteristics, transplant regimens, graft-versus-host disease prophylaxis, and patient care have been published elsewhere.[22] The present report

focuses on the period of hospitalization for SCT. It is the first part of a prospective study in which physical and psychosocial functioning was also comprehensively evaluated at 6, 12, 24, and 36 months after SCT.

As part of the pre-transplant assessment protocol, hematologists first informed their patients about the study assessment of QOL and psychosocial aspects related to SCT. On their admission to the transplantation unit, the research psychiatrist gave detailed information about the protocol design, objectives, and applicability of the study. Patients were assessed in a first structured interview within 48 h of hospital admission (T1, day −9 to day −4, depending on the conditioning regimen), and subsequently on a weekly basis from day of transplant (T2, day 0) until discharge or death (T3, day +7; T4, day +14; T5, day +21 and so on). Similar to the largest prospective report published to date ($n=97$) of psychological and physical data during hospitalization for SCT,[8] in order to limit the number of dropouts (mainly due to hospital discharge), we only used data from the T1 to T4 interviews. In some cases, interviews were conducted within 48 h of the days programmed, either due to scheduling difficulties or because the patient's medical status precluded interview (eg cognitive dysfunction). At hospital admission and subsequently on a weekly basis, a Karnofsky performance status score[23] was obtained from the hematologist. The first interview took 15–45 min and included assessment of sociodemographic data, past psychiatric history, current psychiatric status, overall physical status, overall emotional status, and energy level. After the interview, patients were asked to complete three self-report instruments: the Nottingham Health Profile,[24] the Psychosocial Adjustment to Illness Scale,[25] and the HADS. In the following weekly assessments, we administered a brief structured protocol that lasted 5–15 min. Owing to patient fatigue and concerns about preventing infection, questions in this structured protocol were read aloud and responses written down by the interviewer. This structured interview comprised the assessment of current psychiatric status, overall physical status, overall emotional status, energy level, systemic symptomatology, and HADS.

Three interviewers participated in the study; the main investigator was a psychiatrist (JMP), the two others were a 4th year psychiatric resident (JA) who participated in the study for the first 11 months and a psychiatrist (JB) who participated in the rest of the study. The study was observational by design. Psychiatric care consisted of psychopharmacologic treatment and/or brief psychotherapeutic sessions provided by the corresponding research psychiatrist. Psychiatric intervention could be prompted by referral by the hematologist or by decision of the research psychiatrist in accordance with the hematologist. No attempt was made to influence the amount or type of psychiatric therapy given to patients. The clinical research protocol was reviewed and approved by the Department of Psychiatry's Committee on Clinical Research.

Attrition and missing data

A total of 852 out of 871 possible observations (97.8%). were made from T1 to T4: 220, 217, 214, and 201. Missing observations were due to compromised medical status (3 at T2, 4 at T3, and 6 at T4; six of these 13 missing observations were due to delirium) or due to scheduling difficulties (6 at T4). Attrition was due to hospital discharge (four patients had been discharged by the time of the T4 assessment) and death (two patients had died by the time of the T3 assessment and three by the T4 assessment). The 852 observations were made on the overall physical status and Karnofsky performance status scales. For the systemic symptom scale, we had the same number of observations from T2 to T4 (this scale was not measured at T1). Owing to patient fatigue, in a few cases complete assessment of all instruments could not be performed. The total number of evaluations decreased slightly for psychiatrist-rated depression (851), energy scale (851), and HADS (849).

Statistical analysis

Proportions were compared by using the χ^2 test with Yates correction. Continuous variables were compared by using the Mann–Whitney *U*-test.

To analyze changes in emotional and physical patient-rated measures, we performed a repeated-measures analysis of variance (ANOVA) using a mixed effect modeling procedure that allows for all available data from all patients to be used, rather than the inclusion of only those patients with complete serial data. Time was used as the within-subject factor, type of SCT as the between-subject factor, whereas age, sex, hematological cancer diagnosis, and disease risk status were used as covariates. Owing to the high number of categories of the hematological cancer diagnosis, for ANOVA analysis this variable was categorized into three categories: chronic myelogenous leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia; non-Hodgkin's lymphoma, Hodgkin's disease; and other diagnoses. To test fixed effects, type III *F* tests were used to analyze main effects of the covariates, group, time, and an interaction effect of group × time.

All reported *P*-values are two-tailed. *P*-values were considered significant if they were less than 0.05. For this exploratory study, no adjustment of the alpha level for multiple tests was made. All statistical analyses were conducted with the SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA), with the exception of repeated-measures ANOVA, which was calculated with the PROC MIXED procedure of the statistical package SAS 6.12 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics by type of SCT

Selected demographic and clinical characteristics according to type of SCT are displayed in Table 1. Allogeneic and autologous SCT patients presented different spectra of hematologic diseases; autologous SCT patients were significantly older, were more likely to have intermediate- or high-risk hematologic diseases, were less likely to receive radiotherapy, and were less likely to experience regimen-related toxicity or in-hospital death. Surviving autologous

Table 1 Selected patient characteristics by type of SCT ($n = 220$)

Variable	*Autologous SCT* [a] *(n = 129)*	*Allogeneic SCT (n = 91)*	*P-value*
Age (years)			
Median	45	36	<0.001
Range	16–65	16–55	
Sex, n (%)			
Male	76 (58.9)	53 (58.2)	1.0
Female	53 (41.1)	38 (41.8)	
Hematological cancer diagnosis, n (%)			
Chronic myelogenous leukemia	3 (2.3)	31 (34.1)	<0.001
Acute lymphoblastic leukemia	15 (11.6)	14 (15.4)	
Acute myelogenous leukemia	23 (17.8)	27 (29.7)	
Non-Hodgkin's lymphoma	39 (30.2)	7 (7.7)	
Hodgkin's disease	19 (14.7)	0 (0)	
Multiple myeloma	25 (19.4)	2 (2.2)	
Other cancer diagnoses[b]	5 (3.9)	10 (11.0)	
Disease risk status, n (%)			
Low risk	37 (28.7)	49 (53.8)	0.001
Intermediate risk	23 (17.8)	10 (11.0)	
High risk	69 (53.5)	32 (35.2)	
Conditioning regimen, n (%)			
Chemotherapy only	59 (45.7)	5 (5.5)	<0.001
Chemoradiotherapy	70 (54.3)	86 (94.5)	
In-hospital death, n (%)			
No	126 (97.7)	82 (91.1)	0.03
Yes	3 (2.3)	9 (9.9)	
Regimen-related toxicity score			
Median	2	3	<0.001
Range	0–8	0–10	
Length of stay for survivors (days)[c]			
Median	27	32	<0.001
Range	19–68	21–85	

[a]One syngeneic SCT is included in this group.
[b]For autologous SCT: chronic lymphocytic leukemia ($n = 4$) and granulocytic sarcoma ($n = 1$). For allogeneic SCT: myelodysplastic syndrome ($n = 5$), chronic lymphocytic leukemia ($n = 3$), histiocytosis ($n = 1$), and myeloproliferative syndrome ($n = 1$).
[c]In all, 12 patients were missing due to in-hospital death.

SCT patients also had a significantly shorter length of hospital stay.

Changes in emotional and physical patient-rated measures by type of SCT

The mean scores for emotional and physical outcomes for the overall sample and by type of SCT are shown in Table 2, along with the results of the repeated-measures ANOVA. Complete data from *post hoc* tests are available upon request from the authors. There was a significant main effect of time for all five outcome variables. For the overall sample, anxiety was highest at T1 and decreased afterwards; a marked worsening in physical health status variables (overall physical status, energy level, systemic symptomatology) corresponded with a sharp increase in depression from T1 to T3, and was followed by an improvement in physical health status and a reduction of depression.

Compared to allogeneic SCT, a better physical outcome for autologous SCT was demonstrated by the significant group effect for systemic symptomatology and by the significant group × time interaction for overall physical status and energy level. Allogeneic SCT patients reported significantly higher levels of systemic symptoms than autologous SCT patients did, with *post hoc* tests indicating increasing differences from T2 to T4 ($P = 0.418$ at T2, $P = 0.175$ at T3, and $P = 0.002$ at T4). Examination of Table 2 suggests that the significant type of SCT × time interactions were produced by a more pronounced recovery in overall physical status and energy level for the autologous SCT group evidenced predominantly at T4, although at T1 and T2 their functioning was poorer than allogeneic SCT patients.

There were no significant differences in HADS depression or HADS anxiety between SCT groups. For ease of interpretation and comparison with other studies, results from the HADS are also presented as percentages of cases of anxiety, depression, and anxiety and/or depression from T1 to T4 for the overall sample (Table 3).

Owing to the possible influence of psychopharmacologic treatment, we reanalyzed the HADS anxiety time course

Table 2 Means over time by type of SCT: repeated-measures ANOVA testing of patient-rated emotional and physical measures

Measure (range)	T_1	T_2	T_3	T_4	*Group*		*Time*		*Group × time*	
					F	*P-value*	*F*	*P-value*	*F*	*P-value*
HADS anxiety (0–21)					0.34	0.56	14.08	<0.001	1.89	0.13
Autologous SCT	4.29	3.79	2.63	2.44						
Allogeneic SCT	4.55	3.22	2.80	2.99						
Overall sample	4.40	3.55	2.70	2.66						
HADS depression (0–21)					0.57	0.45	20.87	<0.001	1.34	0.26
Autologous SCT	2.16	4.03	4.24	3.46						
Allogeneic SCT	2.59	4.01	4.65	4.55						
Overall sample	2.34	4.02	4.41	3.91						
Overall physical status (0–10)					0.07	0.79	75.80	<0.001	5.25	0.002
Autologous SCT	7.39	4.91	5.18	6.28						
Allogeneic SCT	7.52	5.29	4.87	5.60						
Overall sample	7.48	5.06	5.05	6.00						
Energy level (0–100)					0.06	0.80	142.27	<0.001	3.01	0.031
Autologous SCT	79.84	50.40	47.12	55.08						
Allogeneic SCT	82.53	55.56	47.87	52.17						
Overall sample	80.95	52.55	47.43	53.88						
Systemic symptoms (0–24)					4.97	0.027	60.58	<0.001	2.58	0.079
Autologous SCT	—	7.65	8.22	5.11						
Allogeneic SCT	—	8.14	9.00	6.71						
Overall sample	7.85	8.54	5.77							

Note: Autologous SCT: T_1 ($n=129$), T_2 ($n=126$–127), T_3 ($n=125$), and T_4 ($n=117$–118). Allogeneic SCT: T_1 ($n=91$), T_2 ($n=90$), T_3 ($n=89$), and T_4 ($n=82$–83). *N* varies because of missing values on some variables. Higher scores on overall physical status and energy level, and lower scores in all other variables represent better functioning. All repeated-measures ANOVA models were adjusted for age, sex, hematological cancer diagnosis, and disease risk status. There was a significant effect of the sex covariate for HADS anxiety, HADS depression, and systemic symptomatology, as well as a significant effect of the disease risk status covariate for energy level.

Table 3 HADS cases at T1, T2, T3, and T4 for the overall sample

HADS cases	*T1 (n=220)*		*T2 (n=216)*		*T3 (n=214)*		*T4 (n=199)*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Anxiety	50	22.7	34	15.7	18	8.4	16	8.0
Depression	25	11.4	35	16.2	45	21.0	33	16.6
Anxiety and/or depression	59	26.8	52	24.1	52	24.3	43	21.6

Note: A case is defined as a score >7 in either the anxiety or depression HADS subscales.

after excluding the 113 patients who received an anxiolytic treatment and the HADS depression time course after excluding the 14 patients who received an antidepressive treatment (data not shown). From a psychiatric point of view, we considered an anxiolytic treatment as 3 consecutive days on benzodiazepines or 14 consecutive days on antidepressants as the minimum treatment periods that could produce a reduction in weekly values of HADS anxiety, and an antidepressive treatment as 14 consecutive days on antidepressants as the minimum period that could produce a reduction in weekly values of HADS depression. After excluding the treated patients, we obtained the same ANOVA statistical results for both HADS anxiety and depression (significant effect for time and nonsignificant for group or group × time interaction) with very similar patterns from T1 to T4 compared with the whole sample of treated and nontreated patients. For the overall sample of nontreated patients, mean scores at T1, T2, T3, and T4 were as follows: HADS anxiety, 3.26, 2.16, 1.93, and 1.80; HADS depression, 2.09, 3.73, 4.27, and 3.76.

There was a significant effect of the sex covariate for HADS anxiety, HADS depression, and systemic symptoms, and a significant effect of the disease risk status covariate for energy level. At every assessment point, women scored higher for anxiety, depression, and systemic symptomatology, while intermediate-risk status patients reported higher energy levels than high-risk status patients did but lower energy levels than low-risk status patients (data not shown).

Discussion

To our knowledge, this is the largest study evaluating various aspects of emotional and physical functioning during hospitalization for SCT. HADS anxiety was at its highest at hospital admission (T1). Although from a medical standpoint this time point is the least risky, the high level of patient anxiety at this time may be reflective of the uncertainty, apprehension, or fearfulness that patients

experience prior to initiating an aggressive medical therapy. A recent review of anxiety in cancer patients[26] highlighted the meaning of events to an individual as an important factor in making people anxious. In our study, the HADS depression temporal course mirrored the physical health patterns for overall physical status, energy level, and systemic symptomatology. A marked worsening in physical health status (after initiating the intensive conditioning treatment) was reflected by a sharp increase in depression levels from T1 to T3; this was then followed by a slight improvement in physical health status and reduction in depression until T4. Among other outcomes, the multivariate predictors of emotional and physical health status variables will be presented in future papers.

Those prospective studies that analyze the time course of anxiety or depression during hospitalization for SCT[4–6,8] differ in terms of the time points selected for assessment and the type of psychological instruments used. Comparison with the present data is therefore difficult. Three of those studies report a pre-transplant assessment, an intermediate time point (all different), and a hospital discharge evaluation, which may vary widely for patients within the same study;[4–6] therefore, they do not provide information that is accurate enough to delineate the time course of those psychological outcomes. Furthermore, in all these studies,[4–6] the results must be interpreted with caution, since only the patients who were interviewed at all assessment points were included in the statistical analysis, thus producing a selection bias in favor of the patients with a better health status. In the largest report published to date ($n=97$),[8] patients were first assessed in a period within 6 months prior to admission and during hospitalization at days -1, $+7$, and $+14$. No mention was made on this study about any psychopharmacologic treatment that could influence the anxiety or depression time course. Anxiety and depression increased from baseline to day -1, reaching the highest level at this time, and then decreased progressively, while physical symptomatology increased gradually from baseline to $+7$ and then decreased until $+14$. Those anxiety, depression, and physical symptomatology patterns can be considered similar to our time-course results. The fact that the baseline assessment for this study[8] was carried out a long time before exposure to the feared situation (hospitalization for SCT) may explain the lower anxiety level at this time point. If we remove this baseline assessment, we find identical patterns in the anxiety time course between that study and our own. Schulz-Kindermann *et al*[27] reported the time course of anxiety and depression during hospitalization at days $+7$, $+14$, and $+21$ ($n=53$), although their study was limited by the lack of a pre-transplant or day 0 assessment. Anxiety and depression did not significantly change over the study period. Comparing our assessments on days $+7$ and $+14$, the patterns we found in the anxiety and depression time course were very similar to those in Schulz-Kindermann *et al*'s study. The level of emotional distress in the transplant patients was slightly lower in this report compared with the only published study using the HADS scale at least in one occasion during hospitalization for SCT.[10] In a prospective study of 131 patients assessed during hospitalization at day $+14$, the level of HADS anxiety was higher than found in our study (autologous SCT: 5.6 *vs* 2.4; allogeneic SCT: 4.3 *vs* 3.0), as was the level of HADS depression (autologous SCT: 6.4 *vs* 3.5; allogeneic SCT: 6.1 *vs* 4.6).

No study published to date has analyzed the time course of any similar construct to our overall physical status or any global QOL measure during hospitalization for SCT. As regards energy level, only one study has reported a measure of fatigue in the SCT setting.[6] Hann *et al* measured fatigue in a sample of 31 autologous SCT patients at 1 week preadmission, day 0, and discharge. Similar to our time-course results on energy level, it was reported that undergoing SCT produced considerable fatigue that tended to increase over the course of treatment.[6]

Regarding the covariate adjustment used in the repeated-measures ANOVA analysis, we found a significant effect of the sex covariate for HADS anxiety, HADS depression, and systemic symptoms, and a significant effect of the disease risk status covariate for energy level. In line with our data, several oncological studies have reported a significant association between female sex and anxiety[28–30] or depression.[30,31] Our results are also consistent with those of other population surveys showing that women tended to report in different QOL questionnaires more symptoms and poorer health than men.[32,33] As expected from a clinical perspective and in agreement with two recent reviews on cancer fatigue,[34,35] we found that increased risk in disease status was associated with decreased energy level.

Compared to their allogeneic SCT counterparts, autologous SCT patients presented a tendency towards a better outcome in physical but not emotional functioning. The fact that autologous SCT patients received a less intensive conditioning treatment may explain these better physical outcomes. The lower in-hospital death rate and lower regimen-related toxicity scores for the autologous SCT group also reflect these differences in the conditioning treatment toxicity. In the only published study analyzing physical symptomatology according to type of SCT, no significant difference was found between SCT groups.[8] In that report, a small sample size ($n=97$) compared to our study and the low proportion of allogeneic SCT patients (only 20% of the total sample) may have reduced the power to detect any statistical significant difference. As for studies that compared autologous and allogeneic SCT patients in terms of depressive and/or anxiety symptoms assessed on at least one occasion during hospitalization for SCT, one study reported a poorer outcome for autologous SCT patients,[4] while other studies did not find significant differences.[8,10,11] In an earlier report from this cohort,[22] we found no significant differences in prevalence rates of DSM-IV psychiatric disorders by type of SCT.

This study has several limitations. First, some of the data were collected using scales constructed specifically for this study because no QOL measure has been validated for use during hospitalization for SCT in adult patients. However, a previous report demonstrated the reliability and validity of the patient-rated QOL instruments devised by the authors.[15] Second, we did not assess systemic symptomatology at T1, so as not to impose an undue burden on our patients. Based on clinical experience and the existing literature, systemic symptoms are at its lowest level

previous to initiating the conditioning treatment at T1.[6–8] Third, we did not measure cognitive function during hospitalization for SCT. Although cognitive dysfunction can affect self-report assessments, we excluded those patients with severe cognitive dysfunction associated with delirium at the time of testing. Fourth, the fact that research psychiatrists also provided psychiatric care may have affected patients' responses to the questionnaires. However, after excluding the patients who received psychopharmacological treatment, the anxiety and depression patterns were very similar throughout the sample of treated and nontreated patients. Fifth, possible benefits from psychiatric treatment on the anxiety and depression time courses cannot be evaluated under the available design. In such an observational sample, comparisons of outcomes based on treatment received are subject to substantial bias. Finally, as in any single-institution study, some conclusions are specific to our center and reflect our patients' characteristics and practice patterns. However, the findings of this study are strengthened by its prospective design, good recruitment rates, large population, use of brief and previously validated instruments, physical and emotional functioning are based on the subjective perception of patients, use of a repeated-measures ANOVA with a mixed effect modeling procedure that allows the use of all available data from all patients. Moreover, because fluctuations in severity and course of physical and psychological symptoms are common, studies using repeated measures at multiple points in time (852 interviews were performed from T1 to T4) may give a more accurate reflection of the physical and psychological functioning during hospitalization for SCT.

Our data illustrate the transient emotional distress that occurs in response to an intensive and demanding medical therapy, and must be distinguished from more persistent problems in psychological adjustment, or frank psychiatric morbidity. In cancer populations, the effect of psychopharmacological and psychological interventions has been reviewed and shown to be beneficial.[26,36,37]

In light of the anxiety and depression temporal trajectory, a comprehensive psychosocial assessment and possibly interventions targeting pre-SCT anxiety that begin prior to admission would represent an ideal approach. Information and education are important in alleviating anxiety, as fears are often based on incorrect information.[26] Owing to the considerable burden imposed on our patients during hospitalization for SCT, the early recognition and treatment of emotional problems would be important. Weekly monitoring of anxiety and depression during hospitalization might help to identify patients who are in need of further psychiatric evaluation and those who might benefit from psychopharmacologic treatment or short-term adjuvant psychological therapy. Development and evaluation of specific interventions should be based on knowledge both of risk factors associated with depression or anxiety as well as the time course of these outcomes. Although it remains to be determined whether early recognition and effective treatment of emotional deficits during the hospitalization period will result in better transplant outcomes, it has the potential to improve medical practice, reduce patient suffering, and enhance QOL.

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4.3 Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation.

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Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation

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ABSTRACT

We have evaluated risk factors associated with fatigue in 220 cancer patients during hospitalization for stem-cell transplantation (SCT). Fatigue was assessed using a validated one-item energy scale and a comprehensive set of fatigue predictors, at hospital admission (baseline), day of SCT, and 7 days and 14 days after SCT. In cross-sectional multivariate analysis, depression was the variable most consistently and strongly associated with fatigue; other factors significantly associated with fatigue at some time during the study included older age, higher education, smoking, lower Karnofsky performance status, loss of appetite, nausea/vomiting, pain, higher regimen-related toxicity, low hemoglobin level, requirement for red blood-cell transfusions, and third year of the study period. In prospective multivariate analysis, baseline depression showed significance or a trend towards significance in its ability to predict subsequent measures of fatigue during hospitalization. Our findings may help to shed light on the mechanisms underlying fatigue and may also guide future interventions.

1. Introduction

Fatigue is one of the most prevalent and distressing symptoms of cancer. Reviews of cancer-related fatigue indicate prevalence rates ranging from 25% to 100% [1–3]. Fatigue has a major negative effect on the patient's quality of life, resulting in substantial adverse physical, psychosocial, and economic/occupational consequences [4–7]. Fatigue is a non-specific, multidimensional construct that is generally thought to involve subjective feelings of tiredness and/or lack of energy. Although research into the condition has increased in the past decade, little in-depth information regarding related clinical factors is available. The literature on this issue has been characterized by methodological limitations [1–3] such as retrospective or cross-sectional designs, sampling bias, use of questionnaires not validated, focus on a limited number of risk factors, use of global emotional distress measures that do not separate depression from anxiety, lack of assessment by multivariate statistical methods, and small sample size.

Haematopoietic stem-cell transplantation (SCT) is a highly aggressive and demanding medical therapy with a profound impact at both physical and psychological levels [8,9]. Only one study has reported clinical correlates of fatigue in patients hospitalized for SCT [6] and in fact their findings were

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limited by the small sample size ($n = 31$) and the lack of assessment by a multivariate statistical method.

In this 3-year prospective in-patient study, we evaluated fatigue using a validated one-item scale and a wide range of potential fatigue risk factors at four consecutive time points during hospitalization for SCT. The purpose of the current paper is to identify multivariate risk factors associated with fatigue during hospitalization for SCT. We hypothesized that depression would be associated with fatigue, even after adjusting for a comprehensive set of clinical confounding variables.

2. Patients and methods

2.1. Study population

The methods have been described in detail elsewhere [9,10]. Briefly, patients were consecutively recruited from the SCT Unit, Hospital Clínic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were haematologic malignancy, age at least 16, patient's first SCT, and verbal informed consent.

2.2. Study variables

2.2.1. Fatigue

Fatigue is a multidimensional concept with several modes of expression: physical (e.g., diminished energy, need to rest), cognitive (e.g., diminished concentration or attention), and affective (e.g., decreased motivation or interest) [1,3]. A methodological problem with regard to the relationship between fatigue and depression is that most depression scales contain items, which overlap with items of the fatigue questionnaires (e.g., energy level, ability to concentrate, and motivation). To solve in part this problem, in the current study, we measured the most physical dimension of fatigue, using energy level as a synonym for this construct. In a previous report, our one-item energy level scale was validated for use as a synonym of the most physical dimension of fatigue during hospitalization for SCT [10]. Patients rated their overall energy loss experienced during the past week in relation to what could be considered their healthy state. The energy loss was rated on a numerical scale from 0 to 100, and the energy level obtained by subtracting the energy loss from 100. In our previous report [10], the reliability and validity of the energy level scale during hospitalization for SCT were demonstrated: (1) we carried out test–retest reliabilities between three consecutive time points during hospitalization for SCT (all $P < 0.001$); (2) convergent validity was tested by examining associations with validated related scales measured at the time of hospital admission (energy and physical mobility scales from the Nottingham Health Profile [11]; all $P < 0.001$); (3) divergent validity was demonstrated by a non-significant association between the energy level scale and a validated unrelated scale measured at the time of hospital admission (health care orientation scale from the Psychosocial Adjustment to Illness Scale [12]; $P = 0.74$); (4) to evaluate criterion validity, we used the method of known-groups comparison to assess the ability of the energy level scale to distinguish between subgroups of patients with different Karnofsky performance status [13] at four different time points during hospitalization for SCT (all $P < 0.001$); (5) we assessed the responsiveness of the energy level scale to changes in Karnofsky performance status from hospital admission to hospital discharge, with the subgroup of patients whose Karnofsky performance status deteriorated the most reporting a significantly worse outcome in energy level ($P < 0.001$) compared to the subgroup of patients with less decline in Karnofsky performance status; and (6) predictive validity was demonstrated by the ability of the hospital admission energy level score to significantly predict hospital discharge energy level score after controlling for other baseline risk factors ($P < 0.001$).

2.2.2. Depression and anxiety

The patient-rated Hospital Anxiety and Depression Scale (HADS) contains two seven-item scales: one for depression and one for anxiety, with higher scores indicating greater distress [14]. Items that may also be attributable to illness or treatment side effects (e.g., fatigue) are not included in this questionnaire. However, in the depression subscale the retardation item ("I feel as if I am slowed down") appears to overlap with fatigue. The HADS scale has been extensively documented in patients with cancer [15–18] and its reliability and validity has been demonstrated [14,15]. Our study used an authorized Spanish translation. Internal consistency, reliability and correlation analysis for the HADS subscales were calculated from T1 to T4. Mean Cronbach's alphas for the depression and anxiety subscales were 0.88 and 0.80, and the mean Spearman rank order correlation between the depression and anxiety subscales was 0.47.

2.2.3. Loss of appetite and insomnia

Potential confounding exists in the measurement of fatigue because of its close association with depression. Since fatigue is primarily a subjectively experienced symptom, self-report measures are the most commonly described type of instrument for measuring fatigue [1]. It arises over a continuum, ranging from tiredness to exhaustion. As a part of our investigation, the nine diagnostic and statistical manual for mental disorders, fourth edition (DSM-IV [19]) criterion items required for the diagnosis of major depression (categorical variable) were rated by the clinician as absent/sub-threshold or present during the past week. The present report uses depression as defined by the HADS and not by DSM-IV because we wanted a depression measure that could be self-reported by the patient, spanning a continuum of depression levels, and not including somatic depressive symptoms such as fatigue or other symptoms that have been found to predict fatigue. One of the nine DSM-IV criterion items to diagnose major depression is fatigue, and two of the other criterion items, insomnia and loss appetite, have been found to predict higher levels of fatigue [1–5,18]. In the current report, we have only used the DSM-IV criterion items insomnia and loss of appetite to study its association with fatigue.

2.2.4. Nausea/vomiting and pain

The systemic symptom scale included the symptoms of vomiting/nausea, diarrhea, dry mouth, mouth pain, abdominalgia, headache, and other pain (the highest score of any other pain if several were present). In a previous report [10], the reliability and validity of the systemic symptom scale during hospitalization for SCT were demonstrated. In this study,

we used only those items that have been found in the literature to be related to fatigue [1–3]. Because odinia represents the main source of pain, we used two pain variables: one specifically for mouth pain and a new composite variable that included the other three pain symptoms of the systemic symptom scale. Symptoms were categorized as absent/mild or moderate/severe. We should state that the systemic symptom scale has not been validated for use with the modifications that the researchers made to include only items related to fatigue.

2.2.5. *Functional status*

The Karnofsky Performance Scale is an index of physical disability developed for the evaluation of oncology patients. Lower scores reflect greater impairment in normal activity, work, and self-care.

2.2.6. *Regimen-related toxicity*

The Bearman Toxicity Scale [20] was used to specifically rate the complications due to chemotherapy or chemoradiotherapy during hospitalization for SCT. Cardiac, bladder, renal, pulmonary, hepatic, central nervous system, gastrointestinal, and stomatitis toxicities are assigned a grade of 0–4 in increasing severity according to specific guidelines for each organ. The regimen-related toxicity score is the sum of the highest toxicity observed in each organ at any time.

2.2.7. *Other disease- and treatment-related data*

Haematological cancer diagnosis, disease risk status (low/intermediate versus high), conditioning regimen (chemotherapy versus chemoradiotherapy), type of SCT (autologous or syngeneic versus allogeneic), haemoglobin count, period of study entry (July 1994–June 1996 versus July 1996–August 1997), weekly requirement of red blood cell transfusions, and weekly requirement of opioid and benzodiacepine medications. Morphine and additional analgesics were converted to morphine equivalents using the conversion factors of Stimmel [21] and benzodiacepines medications were converted to diazepam equivalents [22].

2.3. *Study procedures*

Patients were assessed in a first structured interview within 48 h of hospital admission (T1, day −9 to day −4 depending on the conditioning regimen), and subsequently on a weekly basis from day of transplant (T2, day 0) until discharge or death (T3, day +7; T4, day +14; T5, day +21, and so on). In order to limit the number of dropouts (mainly due to hospital discharge) we only used data from the T1 to T4 interviews. At hospital admission and subsequently on a weekly basis, a Karnofsky performance status score was obtained from the haematologist. No inter-rater reliability assessment was carried out for this performance status measure. All structured interviews were carried out by three researchers: the main investigator was a psychiatrist (J.M.P.), the two others were a fourth year psychiatric resident (J.A.) who participated in the study for the first 11 months and a psychiatrist (J.B.) who participated in the rest of the study. Each patient was interviewed by only one of the researchers during the hospitalization period. The first interview included sociodemographic data, assessment of psychiatric status with DSM-IV criteria, energy level scale, and the HADS. After this first interview, patients were asked to complete two self-report instruments: the Nottingham Health Profile to measure health-related quality of life and the Psychosocial Adjustment to Illness Scale to assess psychosocial adaptation. In the following weekly assessments, we administered a structured interview that comprised assessment of psychiatric status with DSM-IV criteria, energy level scale, systemic symptom scale, and the HADS. After discharge, using a standardized form, J.M.P. abstracted medical data from hospital charts. The regimen-related toxicity, requirement of red blood cell transfusions, opioid treatment, and benzodiacepine treatment were obtained from T2 to T4. The clinical research protocol was reviewed and approved by the Department of Psychiatry's Committee on Clinical Research.

2.4. *Statistical analysis*

Univariate and multivariate linear regression analysis were used to identify predictors of energy level at T1, T2, T3, and T4. We dichotomized all weekly Karnofsky performance status variables (lowest quintile versus upper four quintiles), and all weekly benzodiazepine treatment variables (lower four quintiles versus highest quintile) because of their highly skewed distributions. Because their median energy levels were very similar, the time periods July 1994–June 1995 and July 1995–June 1996 were combined in the same category. For multivariate models, a stepwise selection method was used to select significant variables. Since poor health status can significantly increase both depression and fatigue [1–3,23,24], interaction terms between HADS depression and disease risk status, admission hemoglobin level, Karnofsky performance status, regimen-related toxicity, mouth pain, other pain, and requirement of red-blood cell transfusions were tested in their corresponding multivariate models. All multivariate models were adjusted for sex and age. Collinearity was assessed using variance inflation factors and standard residuals-based diagnostic procedures were used to assess model assumptions and adequacy of the model fit. Performance of the model was assessed by the adjusted explained variance (R^2). Patients with missing data on any scale were excluded from analyses. All reported P values are two-tailed. P values were considered significant if they were less than 0.05. No adjustment of the alpha level for multiple tests was made. Statistical analyses were done with SPSS (version 11.5).

2.5. *Attrition and missing data*

A total of 852 out of 871 possible observations (97.8%) were made from T1 to T4: 220, 217, 214, and 201. Missing observations were due to compromised medical status (3 at T2, 4 at T3, and 6 at T4) or scheduling difficulties (6 at T4). Attrition was due to hospital discharge (four patients had been discharged before the T4 assessment) and death (two patients had died by the time of the T3 assessment and 3 by the T4 assessment). Due to patient fatigue, in a few cases complete assessment of all predictor variables could not be performed. The total number of evaluations for energy level, loss of appetite, insomnia, and HADS decreased to 851, 851, 851 and 849,

respectively. For the haemoglobin count, information was missing from two patients.

3. Results

Of 253 patients that received SCT during the 3-year recruitment period, 235 met the eligibility criteria. Due to scheduling difficulties, 15 patients could not be interviewed at the first assessment and were excluded from the study. All patients who were approached agreed to be interviewed. Thus, the final study cohort included 93.6% of the eligible population (220/235). There were no differences in age, sex, haematologic diagnosis, or disease risk status between the 220 patients who participated in the study and the 15 excluded patients ($P > 0.20$). Baseline patient characteristics are displayed in Table 1. Measures in energy level and 12 fatigue risk factors from day of hospital admission (T1) to day +14 after SCT (T4) are listed in Table 2. Median energy level scores at T1, T2, T3, and T4 were 80, 50, 50 and 50, respectively.

Table 3 shows all tested univariate predictors of energy level from T1 to T4. Variables with $P < 0.10$ in univariate analysis were included in multivariate linear regression models. Full multivariate models estimating energy level from T1 to T4 (Table 4) included baseline data in addition to concurrent weekly values of those variables measured over time. Furthermore, the T1 energy level variable was incorporated in the full regression models used to predict energy level at T2, T3 and T4, to adjust for the effect of this variable at baseline. Adjusted explained variance for all these models ranged from 32% to 48%. After adjusting for the effect of other risk factors, low Karnofsky performance status at T1 and higher HADS depression at T2, T3, and T4 were the factors with the strongest association with low energy level in their corresponding regression models. Baseline multivariate models were used to study the predictive effect of those T1 risk factors on energy level at T2, T3, and T4 (Table 5). Compared to full multivariate models, a lower number of variables contributed to explaining the adjusted variance (range 6–19%). Baseline energy level was the strongest and most consistent predictor of subsequent measures of energy level. Baseline HADS depression was found to significantly predict T3 energy level ($P = 0.038$), showing a trend for significance in predicting T2 ($P = 0.093$) and T4 ($P = 0.16$) energy level. Tested interaction terms did not reach statistical significance in any full or baseline multivariate model (data not shown).

To investigate any confounding effect of the original HADS depression scale due to the fact that it contains the retardation item ("I feel as if I am slowed down") which appears to overlap with fatigue, we excluded this item from the scale and repeated the multivariate analysis. Although there was a reduction in the standardized β coefficients of the HADS depression after excluding this item (data not shown), we obtained the same significant results in predicting energy level in the full and baseline multivariate models.

To further explore the complex relation between fatigue and depression, we performed univariate and multivariate regression analyses to identify predictors of HADS depression from T1 to T4 (data not shown). For these analyses we used the same candidate risk factors as for the analyses predicting energy level. While low energy level was significantly associated with higher HADS depression in all corresponding multivariate full models, baseline energy level had no effect on

Table 1 – Baseline patient characteristics

Characteristic	T1 ($n = 220$)
Age (years)	38 (16–65)
Female sex, *n* (%)	91 (41.3)
Married/cohabitating, *n* (%)	141 (64.1)
Education, years	11 (4–12)
Current smoking, *n* (%)	41 (18.6)
Haematological cancer diagnosis, *n* (%)	
Acute myelogenous leukemia	50 (22.7)
Acute lymphoblastic leukemia	29 (13.2)
Chronic myelogenous leukemia	34 (15.5)
Non-Hodgkin's lymphoma	46 (20.9)
Hodgkin's disease	19 (8.6)
Multiple myeloma	27 (12.3)
Other[a]	15 (6.8)
High risk disease status, *n* (%)	100 (45.5)
Hemoglobin count (g/dl)	115 (62–159)
Chemoradiotherapy, *n* (%)	156 (70.9)
Allogeneic SCT,[b] *n* (%)	129 (58.6)
July 1996–August 1997, *n* (%)	75 (34.1)

Data are median (range) unless otherwise indicated. Comparison categories can be found in Section 2.2 and missing information in Section 2.5.
a Chronic lymphocytic leukemia ($n = 7$), myelodysplastic syndrome ($n = 5$), histiocytosis ($n = 1$), myeloproliferative syndrome ($n = 1$), and granulocytic sarcoma ($n = 1$).
b One syngeneic SCT was placed with the autologous SCT group.

Table 2 – Patient characteristics over time

Characteristic	T1 ($n = 220$)	T2 ($n = 217$)	T3 ($n = 214$)	T4 ($n = 201$)
Energy level score	85 (0–100)	50 (0–100)	50 (0–100)	50 (20–100)
Karnofsky score	100 (50–100)	70 (40–80)	70 (30–80)	70 (40–90)
HADS anxiety score	3 (0–21)	2 (0–17)	2 (0–16)	2 (0–17)
HADS depression score	1 (0–19)	3 (0–20)	3 (0–17)	3 (0–20)
Loss of appetite, *n* (%)	22 (10.0)	176 (81.5)	181 (84.6)	151 (75.1)
Insomnia, *n* (%)	23 (10.5)	55 (25.5)	53 (24.8)	39 (19.4)
Nausea/vomiting, *n* (%)		150 (69.1)	110 (51.4)	65 (32.3)
Mouth pain, *n* (%)		27 (12.4)	128 (59.8)	52 (25.9)
Other pain, *n* (%)		80 (36.9)	69 (32.2)	31 (15.4)
Regimen-related toxicity score		1 (0–4)	2 (0–6)	2 (0–8)
Red blood cell transfusions, *n*		0 (0–10)	2 (0–10)	2 (0–8)
Opioid treatment		0 (0–82)	9 (0–350)	21 (0–439)
Benzodiazepine treatment		0 (0–67)	0 (0–118)	2 (0–118)

Data are median (range) unless otherwise indicated. See Section 2.2 for comparison categories and Section 2.5 for missing information. Opioid treatment is expressed in mg of morphine equivalents and benzodiazepine treatment in mg of diazepam equivalents. Higher scores on energy level and Karnofsky scales and lower scores in all other scales represent better functioning.

Table 3 – Univariate predictors of energy level at T1, T2, T3, and T4

	T1 energy level (n = 220)	T2 energy level (n = 216)	T3 energy level (n = 214)	T4 energy level (n = 201)
T1 risk factors				
Age	−0.096	−0.060	−0.070	−0.086
Female	−0.031	−0.027	−0.061	−0.067
Married/cohabitating	0.077	0.011	0.141*	0.041
Education	0.095	0.026	−0.119*	−0.037
Current smoking	−0.122*	−0.033	−0.073	−0.074
High risk disease	−0.239***	−0.068	−0.159*	−0.111
Hemoglobin count	0.252***	0.101	0.202**	0.178*
Chemoradiotherapy	0.033	0.075	0.026	0.020
Allogeneic SCT	0.062	0.104	0.018	−0.077
July 1996–August 1997	0.259***	0.308***	0.204**	0.184**
HADS anxiety	−0.259***	−0.204**	−0.206**	−0.158*
HADS depression	−0.453***	−0.253***	−0.267***	−0.216**
Karnofsky status	0.484***	0.235***	0.224***	0.114
Loss of appetite	−0.429***	−0.141*	−0.118*	−0.097
Insomnia	−0.393***	−0.229***	−0.178**	−0.102
T2–T4 risk factors				
HADS anxiety		−0.247***	−0.266***	−0.380***
HADS depression		−0.482***	−0.573***	−0.513***
Karnofsky status		0.348***	0.337***	0.372***
Loss of appetite		−0.359***	−0.135*	−0.194**
Insomnia		−0.239***	−0.075	−0.243***
Nausea/vomiting		−0.251***	−0.304***	−0.223**
Mouth pain		−0.114*	−0.107	−0.244***
Other pain		−0.133*	−0.286***	−0.243***
Regimen-related toxicity		−0.158*	−0.213*	−0.216**
Red blood-cell transfusions		−0.055	−0.229***	−0.064
Opioid treatment		−0.103	−0.164*	−0.146*
Benzodiazepine treatment		−0.018	−0.118*	−0.163*

Each energy level outcome was analyzed for baseline T1 data in addition to concurrent weekly values of those risk factors measured from T2 to T4. Data are expressed as standardized β coefficients. See also footnote in Table 2.

* $P < 0.10$.

** $P < 0.01$.

*** $P < 0.001$.

predicting subsequent HADS depression at T2 ($P = 0.68$), T3 ($P = 0.50$), and T4 ($P = 0.74$) in multivariate baseline models.

4. Discussion

To our knowledge, this study is the largest in-hospital investigation studying risk factors for fatigue in any cancer sample. In cross-sectional multivariate analysis, depression was the variable most consistently and strongly associated with fatigue. Although there are some contradictory results [7,25,26], most studies have emphasized a significant cross-sectional association between depression and fatigue [5,6,16–18]. Failure to find a significant association may partly be explained by the nature of the patient sample and/or a low depression level. Stone and colleagues [25] found that depression had no effect on fatigue in a sample of patients with advanced disease and a very short prognosis. Under these circumstances, the role of depression may be more difficult to detect because of the strong cancer- or treatment-related biological processes at that moment. In another study [26], depression was not associated with fatigue in a sample of long-term cancer survivors with a low prevalence of depression. Visser and Smets [7] concluded that fatigue and depression were unrelated conditions with different patterns over time. However, in a recent study Tchekmedyian and colleagues [27] reported that improvement of fatigue was significantly associated with a reduction in depression.

Fatigue can occur as a symptom of depression [5,19,23,24] or, alternatively, it may precipitate feelings of depression because of its adverse effect on mood and functional ability. In our cross-sectional multivariate analysis, HADS depression was found to predict energy level, and energy level was found to predict HADS depression. However, in prospective multivariate analysis, baseline HADS depression showed significance or a trend towards significance for predicting subsequent measures of energy level, while baseline energy level did not predict subsequent measures of HADS depression. In addition, medical complications or treatment side effects that can significantly impact on fatigue may also cause or mimic depression [1–3,23,24]. However, our depression measure did not include somatic symptoms that could be attributed to illness or treatment side effects, and statistical analyses controlled for a comprehensive set of clinical confounding factors.

Table 4 – Full multivariate models: predictors of energy level at T1, T2, T3, and T4

	β	P	Adjusted R^2
T1 energy level ($n = 218$)			0.454
T1 Karnofsky	0.332	<0.001	
T1 loss of appetite	−0.263	<0.001	
T1 HADS depression	−0.214	<0.001	
July 1996–August 1997	0.193	0.001	
Current smoking	−0.148	0.010	
Hemoglobin count	0.123	0.032	
Age	−0.110	0.037	
T2 energy level ($n = 216$)			0.402
T2 HADS depression	−0.310	<0.001	
T1 energy level	0.212	<0.001	
T2 Karnofsky	0.176	0.002	
T2 nausea/vomiting	−0.161	0.004	
July 1996–August 1997	0.135	0.028	
T2 loss of appetite	−0.128	0.038	
T3 energy level ($n = 212$)			0.469
T3 HADS depression	−0.434	<0.001	
July 1996–August 1997	0.187	<0.001	
T3 other pain	−0.164	0.003	
Education	−0.159	0.003	
T1 energy level	0.153	0.006	
T3 red blood cell transfusions	−0.137	0.009	
T3 regimen-related toxicity	−0.135	0.012	
T4 energy level ($n = 199$)			0.321
T4 HADS depression	−0.440	<0.001	
July 1996–August 1997	0.154	0.016	
T4 Karnofsky	0.156	0.019	

All variables with $P < 0.10$ in univariate analysis were included in multivariate regression models. Only significant ($P < 0.05$) predictors are listed. See also footnote in Table 2.

Table 5 – Baseline multivariate models: predictors of energy level at T2, T3, and T4

	β	P	Adjusted R^2
T2 energy level ($n = 216$)			0.190
T1 energy level	0.329	<0.001	
July 1996–August 1997	0.229	0.001	
T3 energy level ($n = 212$)			0.150
T1 energy level	0.223	0.004	
Education	−0.170	0.010	
July 1995–June 1996	0.158	0.020	
T1 HADS depression	−0.152	0.038	
T4 energy level ($n = 199$)			0.058
T1 energy level	0.249	<0.001	

P values for T1 HADS depression at models T2 and T4 were 0.093 and 0.16. See also footnote in Table 4.

As expected from a clinical perspective and in agreement with other reports, we found that older age [16,26], lower Karnofsky performance status [4], higher disease or treatment burden [26], anaemia (low haemoglobin level/requirement of red-blood cell transfusions) [4,28], pain [5,17,25], or gastrointestinal symptoms such as nausea/vomiting [4] or loss of appetite [4] are significantly associated with fatigue. Pain can occur secondary to anticancer treatment and may lead to fatigue through its effects on mood, activity level, and/or sleep [5]. Fatigue may also be induced by loss of nutrients as a result of anorexia, nausea or vomiting [1].

Another noteworthy finding in this study was the significant association between smoking at the time of hospital admission and low energy level, even after adjusting for other clinical confounding variables. Consistent with our findings, several studies in the general population have described an association between smoking and fatigue [29,30]. We also found that degree of fatigue decreased in the last year of our study period, probably in relation to improvement in supportive care technologies and better patient selection. Our finding that higher education attainment, a surrogate of higher socioeconomic status [31], was predictive of lower energy level was contrary to expectations.

This study has several limitations. First, we did not perform a multidimensional assessment of fatigue. However, the advantages of the single-item fatigue scale include low burden to patients, simplicity, and ease of clinical use. Administering quality of life instruments in the SCT setting needs to be done with an acute awareness of the risk of patient overload. Second, although we did not measure inter-rater reliability for the haematological ratings of the Karnofsky performance status, our accurate knowledge of the patients' physical and functional status coupled with the use of strict guidelines for the assessment aided our estimation of performance status ratings. Third, we did not assess systemic symptomatology at T1, so as not to impose an undue burden on our patients. Based on clinical experience and the existing literature, systemic symptoms are at their lowest level previous to initiating the conditioning treatment at T1 [6,8]. Fourth, although our results provide support for the prognostic importance of depression, they do not establish that depression causes fatigue. To establish a causal relationship, we need longitudinal research combining repeated measurement of depression and its presumed pathophysiological mechanisms, followed by adequately powered, randomized trials targeting the implicated mechanisms. Finally, as in any single-institution study, some conclusions are specific to our center and reflect our patient characteristics and practice patterns. However, the findings of this study are strengthened by its prospective design, non-biased sample, high recruitment rates, large population, use of brief and previously validated instruments, use of serial evaluations, and use of multivariate regression models that included a comprehensive set of clinical confounding variables.

Our results support the multidimensional etiology of fatigue and may be useful in generating hypotheses about mechanisms underlying fatigue and directing intervention efforts for cancer-related fatigue. Although some clinical factors that we have found to be associated with fatigue are non-modifiable, other factors are treatable and may result in a decrease of fatigue levels. From a clinical perspective, we highlight the importance of carefully screening for depression in cancer patients who complain of fatigue. Short and simple self-reported questionnaires, such as the HADS, may help to detect depression in the clinical setting [15,16]. Many of the depressed patients can be treated effectively with medication and/or psychotherapy [1–3,23,24]. Furthermore, appropriate

treatment of pain, nausea/vomiting, or anaemia may be effective for reducing fatigue. In addition, help from smoking cessation services early in the disease process may have a role in promoting physical and psychological health. If this is not possible, evident restrictions for smoking during hospitalization for SCT provide an important opportunity for initially refractory patients to stop smoking. Clearly, further research is needed to gain a better understanding of the physiopathology and treatment of fatigue in cancer patients [1–3]. Among other outcomes, the course and predictors of fatigue during post-SCT follow-up and their impact on quality of life will be presented in future articles.

Conflict of interest statement

There is no any financial or personal relationship with other people or organisations that could inappropriately influence (bias) the authors' work.

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4.4 Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation.

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Psychiatric Morbidity and Impact on Hospital Length of Stay Among Hematologic Cancer Patients Receiving Stem-Cell Transplantation

By Jesús M. Prieto, Jordi Blanch, Jorge Atala, Enric Carreras, Montserrat Rovira, Esteve Cirera, and Cristóbal Gastó

Purpose: **To determine the prevalence of psychiatric disorders during hospitalization for hematopoietic stem-cell transplantation (SCT) and to estimate their impact on hospital length of stay (LOS).**

Patients and Methods: **In a prospective inpatient study conducted from July 1994 to August 1997, 220 patients aged 16 to 65 years received SCT for hematologic cancer at a single institution. Patients received a psychiatric assessment at hospital admission and weekly during hospitalization until discharge or death, yielding a total of 1,062 psychiatric interviews performed. Psychiatric disorders were determined on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Univariate and multivariate linear regression analyses were used to identify variables associated with LOS.**

Results: **Overall psychiatric disorder prevalence was 44.1%; an adjustment disorder was diagnosed in 22.7% of patients, a mood disorder in 14.1%, an anxiety disorder in 8.2%, and delirium in 7.3%. After adjusting for admission and in-hospital risk factors, diagnosis of any mood, anxiety, or adjustment disorder ($P = .022$), chronic myelogenous leukemia ($P = .003$), Karnofsky performance score less than 90 at hospital admission ($P = .025$), and higher regimen-related toxicity ($P < .001$) were associated with a longer LOS. Acute lymphoblastic leukemia ($P = .009$), non-Hodgkin's lymphoma ($P = .04$), use of peripheral-blood stem cells ($P < .001$), second year of study ($P < .001$), and third year of study ($P < .001$) were associated with a shorter LOS.**

Conclusion: **Our data indicate high psychiatric morbidity and an association with longer LOS, underscoring the need for early recognition and effective treatment.**

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HEMATOPOIETIC stem-cell transplantation (SCT) is rapidly becoming a part of conventional cancer treatment. Today, over 350 centers in Europe perform more than 18,000 stem-cell transplants a year.[1] Although SCT is able to cure a variety of malignant and nonmalignant diseases, the procedure is still associated with significant morbidity and mortality.[1,2]

Research investigating the impact of this highly aggressive procedure on quality of life and psychosocial issues has increased in recent years. Many studies have been performed 1 to 10 years after SCT[2] and have examined the problems associated with long-term adjustment, but have not investigated the impact during hospitalization for SCT. A few longitudinal studies that include hospitalization and post-SCT assessments indicate that it is during the hospitalization period when individuals often experience greater psychological distress.[3-5] In the only published study of psychiatric morbidity using standardized diagnostic criteria during hospitalization for SCT, a psychiatric disorder was diagnosed in 41% of 39 allogeneic SCT patients.[6]

Reviews of depression[7,8] or anxiety[9] among different cancer populations indicate that prevalence rates of these disorders remain uncertain because of limitations in research methodology: depression ranged from 1% to 53% and anxiety ranged from 1% to 44%. Methodologic inadequacies included the use of self-report questionnaire scores at a level suggestive of a clinical diagnosis without using standardized diagnostic criteria, the use of retrospective chart reviews, biased samples, or small sample sizes.[7-9] Although self-report scales do not measure prevalence of disorders, ratings of depressive and anxiety symptoms from the patient's perspective are considered very valuable because these are subjectively experienced symptoms. Because of the limitations of different methods for psychiatric evaluation, the most accurate assessment would include self-report, psychiatric interview, and chart review taken together.

Psychiatric morbidity can adversely affect patients in many ways: it can impair quality of life,[10] functional status,[11] and energy level[12]; increase symptom burden and pain intensity[13-15]; interfere with medical treatment[16-18]; and possibly reduce overall survival time.[19-21] Furthermore, in diverse medical populations and after adjusting for

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potential confounders, psychiatric morbidity has been associated with higher health care costs[22,23] and increased hospital length of stay (LOS).[24] Previous studies of the impact of psychiatric morbidity on LOS present methodologic limitations such as lack of use of standardized psychiatric diagnostic criteria, retrospective or cross-sectional designs, lack of controlling for potential confounding variables such as disease or treatment-related factors, or small sample size. To our knowledge, no studies adjusting for potential confounding variables have evaluated whether psychiatric morbidity has an impact on LOS in the SCT setting.

These above-mentioned complications associated with psychiatric disorders, coupled with the substantial emotional suffering, and the fact that psychiatric disorders tend to be underecognized,[8,9,25] highlight the critical importance of identifying and treating these disorders in transplant patients. Knowledge of psychiatric morbidity in the SCT setting may contribute to early identification of those disorders and to the design of appropriate prevention and treatment strategies.

In this 3-year prospective inpatient study, we evaluated the psychiatric morbidity as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[26] (DSM-IV) during hospitalization for SCT. We tested the hypothesis that, compared with individuals without psychiatric disorders, patients with psychiatric disorders would have a longer LOS, even after adjusting for other disease- or treatment-related variables.

PATIENTS AND METHODS

Study Population

Patients were consecutively recruited from the SCT Unit, Hospital Clínic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were hematologic malignancy, at least 16 years of age, patient's first SCT, and verbal informed consent. Of 253 patients that received an SCT, 235 met the eligibility criteria. Because of scheduling difficulties, 15 patients could not be interviewed. All patients who were approached agreed to be interviewed. Thus, the final study cohort included 93.6% of the eligible population (220 of 235).

Conditioning Regimens, Graft-Versus-Host Disease Prophylaxis, and Patient Care

A variety of conditioning regimens were used during the study period, chosen on the basis of transplant type and hematologic cancer. Most of the allogeneic SCT patients received cyclophosphamide and total-body irradiation unless contraindicated by prior irradiation, in which case they received busulfan/cyclophosphamide. Autologous SCT patients received cyclophosphamide/total-body irradiation, melphalan/total-body irradiation, carmustine/etoposide/cytarabine/cyclophosphamide, carmustine/etoposide/cytarabine/melphalan, or melphalan. For allogeneic SCT patients, graft-versus-host disease prophylaxis consisted of short-course methotrexate and cyclosporine with or without methylprednisolone, or T-cell depletion and cyclosporine with or without methylprednisolone.

All patients were assisted in laminar airflow rooms and received *Pneumocystis carinii*, viral, bacterial, and fungal prophylaxis according to institutional protocols. Discharge criteria, which did not change over the course of the study, included engraftment, adequate oral intake, and control of medical problems.

Study Procedures

The present report focuses on hospitalization for SCT, the initial analysis of a prospective study in which physical and psychosocial functioning was also comprehensively evaluated at 6, 12, 24, and 36 months after transplantation. As part of the pretransplant assessment protocol, hematologists first informed their patients about the study assessment of quality of life and psychosocial aspects related to SCT. On their admission to the transplantation unit, the research psychiatrist gave detailed information about the protocol design, objectives, and applicability of the study. Patients were assessed in a first structured interview within 48 hours of hospital admission (day −9 to day −4, depending on the conditioning regimen), and subsequently on a weekly basis from day of transplant (day 0) until discharge or death (days +7, +14, +21 and so on). Before the first interview, a Karnofsky functional status score[27] was obtained from the hematologist. The first interview lasted 15 to 45 minutes and included sociodemographic data, past psychiatric history, current psychiatric status, and one-item patient-rated instrument assessing overall physical health and another one-item patient-rated instrument assessing overall emotional health. In those one-item instruments devised by the researcher, patients were asked to rate their overall physical or emotional health experienced during the past week according to a 0 to 10 numeric rating scale. The scales were anchored at 0 with the statement "very poor" and at 10 with the statement "excellent." After the interview, patients were asked to complete three self-report instruments: the Nottingham Health Profile,[28] to measure health-related quality of life; the Psychosocial Adjustment to Illness Scale,[29] to assess psychosocial adaptation; and the Hospital Anxiety and Depression Scale,[30] to evaluate psychological distress. In the following weekly assessments, we administered a brief structured protocol that lasted 5 to 15 minutes. This structured interview comprised assessment of current psychiatric status, patient-reported physical symptoms (investigator-constructed), patient-rated physical health, patient-rated emotional health, and the Hospital Anxiety and Depression Scale. After discharge, and using a standardized form, the first author (J.M.P) abstracted medical diagnoses, laboratory results, vital signs, psychotropic treatment, and pertinent clinical data required to rate the regimen-related toxicity scale.[31] The data abstractor was not formally blinded to the LOS of each subject.

Three interviewers participated in the study; the main investigator was a psychiatrist (J.M.P), the two others were a fourth-year psychiatric resident (J.A) who participated in the study for the first 11 months and a psychiatrist (J.B) who participated in the rest of the study. Psychiatric information from the patient interviews was complemented with information from the family and medical and nursing staff. Psychiatric diagnoses were assigned at a diagnosis meeting held every 2 months, at which a consensus diagnosis was reached on each patient. No interrater reliability assessment was carried out.

The study was naturalistic by design. Psychiatric care consisted of psychopharmacologic treatment and/or brief psychotherapeutic sessions provided by the corresponding research psychiatrist. Psychiatric intervention could be prompted by referral by the hematologist or by decision of the research psychiatrist in accordance with the hematologist. No attempt was made to influence the amount or type of

psychiatric therapy given to patients. The clinical research protocol was reviewed and approved by the Department of Psychiatry's Committee on Clinical Research.

Psychiatric Assessment

The psychiatric interview followed a structured format, with psychiatric diagnoses being defined according to DSM-IV criteria. Our purpose was to have a relatively short psychiatric interview, which focused on mood, anxiety, and adjustment disorders known to be common in cancer patients.[6-9,32] Details of past psychiatric history interview will be reported elsewhere.

Current psychiatric status. In a checklist format, the DSM-IV criterion items required for the diagnosis of a major depressive episode and adjustment disorder were rated during the interview by the clinician as absent, subthreshold, or present during the past week. As for anxiety disorders, we used screening questions relevant to panic disorder, generalized anxiety disorder, phobia, and obsessive-compulsive disorder, and in case of positive findings, full criteria were ascertained. Although alcohol and smoking histories were also obtained, we did not include specific questioning for abuse or dependence criteria. The DSM-IV requires a symptom to be counted toward the diagnosis of major depressive episode only if it is thought not to be attributable to cancer itself or to the conditioning treatment. Because five out of a list of nine criteria are required for diagnosis, the DSM-IV presents a risk of underdiagnosis. In the current report, we used the model of the Sloan-Kettering group to diagnose a major depressive episode, which is recommended for research purposes.[33] This modified DSM-IV approach eliminates anorexia and fatigue from the list of nine criteria, and requires only four of the remaining seven symptoms for diagnosis. This approach ensures the most homogeneous depressed group possible, with the fewest confounding variables, thereby increasing the clinical and statistical significance of the research data.[33]

Psychiatric rates by time of diagnosis and overall prevalence rates. Depending on the time of psychiatric diagnosis, we distinguish admission prevalence from postadmission incidence. Admission prevalence is the rate at which existing disorders are diagnosed at hospital admission (first interview). Postadmission incidence is the rate at which new disorders occur during in-hospital follow-up (from the second interview until discharge or death). Overall prevalence is the rate at which existing disorders are diagnosed during the hospitalization period (from hospital admission until discharge or death). Postadmission prevalence at any specific weekly interview is the rate that will include those psychiatric disorders that currently meet diagnostic criteria (whenever first diagnosed at this interview or not).

Instruments

Because this article's focus is on psychiatric morbidity, detailed description and results corresponding to other instruments mentioned under Study Procedures will be reported elsewhere.

Functional status. The Karnofsky Performance Scale[27] is a widely accepted index of physical disability developed for the evaluation of oncology patients. Patients are rated in deciles from 0 to 100, with lower scores reflecting greater impairment in normal activity, work, and self-care.

Regimen-related toxicity. The Bearman Toxicity Scale[31] is used to rate the complications caused by chemotherapy or chemoradiotherapy. When toxicity can be attributed to infection, graft-versus-host disease, bleeding, or side effects of noncytotoxic treatment, that toxicity is excluded. Cardiac, bladder, renal, pulmonary, hepatic, CNS, gastrointestinal, and stomatitis toxicities are assigned a grade of 0 to 4 in increasing severity according to specific guidelines for each organ. The regimen-related toxicity score assigned to each patient is the sum of the highest toxicity observed in each organ at any time.

Other Study Variables

LOS. Depending on the conditioning regimen, patients were admitted from day −9 to day -4 (92.7% were admitted from day −8 to day −6). For this reason, we used as an outcome measure LOS as defined by the number of overnight stays from day of transplantation (day 0) until hospital discharge.

Sociodemographics. Characteristics assessed were age, sex, ethnicity, marital status, and educational attainment.

Disease- and treatment-related data. Variables included hematologic cancer diagnosis, time since cancer diagnosis, conditioning regimen, source of stem cells, and type of SCT. One potential time-related influence affecting LOS over a 3-year period was practice variations. We included in our analyses a variable encoding the year of study as an adjustment for practice variations. On the basis of prior research,[34] patients were divided according to their disease risk status. Low-risk patients had myelofibrosis, chronic myelogenous leukemia in chronic phase, or were in first complete remission from any disease. High-risk patients were partially responsive, had refractory disease, or were in relapse at the time of transplantation. Patients with myelodysplastic syndromes were defined as high risk, in case of life-threatening hemorrhage or infection and/or refractoriness to platelet transfusions. Intermediate-risk patients were having at least second completed responses or chronic myelogenous leukemia in accelerated phase. In-hospital complications included acute graft-versus-host disease,[35] veno-occlusive disease,[36] and presence of documented bacterial, fungal, or viral infections.

Statistical Analysis

Data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed variables are reported as mean and range (minimum to maximum). Skewed distributed variables are presented as median and range. Proportions were compared by using the χ^2 test with Yates correction or Fisher's exact test; continuous variables were compared by parametric (*t* test and analysis of variance) or nonparametric (Mann-Whitney *U* and Kruskal-Wallis tests) statistics, as appropriate.

To examine the impact of psychiatric disorders on LOS for those patients surviving until hospital discharge, we used univariate and multivariate linear regression analysis. By using χ^2 test with Yates correction, we compared proportions of patients diagnosed with any overall delirium, any overall mood disorder, any overall anxiety disorder, or any overall adjustment disorder by type of SCT and we found no statistically significant differences. Therefore, the decision was made to analyze the data set as a single sample. Because of the consistently higher median LOS for patients with a mood, anxiety, or adjustment disorder compared with patients without a psychiatric disorder, the frequent coexistence of depressive and anxiety symptoms,[7,9] and our aim to increase sample size in order to reduce the possibility of a type II error, we pooled those three disorders into a composite variable including any mood, anxiety, or adjustment disorder. We examined the impact on LOS of the composite variable as well as considering those three diagnoses as separate disorders. As all mood, anxiety, or adjustment disorders diagnosed at hospital admission had been present during at least some part of in-hospital follow-up, we considered the overall prevalence of any mood, anxiety, or adjustment disorder as an in-hospital risk factor. Those surviving patients (n =

208) that were diagnosed with any mood, anxiety, or adjustment disorder at any time during the hospitalization period (admission or in-hospital follow-up) were considered as having overall mood, anxiety, or adjustment disorder.

Admission and in-hospital risk factors used to study its association with LOS were chosen a priori, on the basis of past work in the field and because of clinical relevance.[24,34] Admission risk factors included age (continuous variable), sex, Karnofsky score (90-100 *v* < 90), hematologic cancer diagnosis (acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and other), disease risk status (low, intermediate, and high), conditioning regimen (chemotherapy *v* chemoradiotherapy), type of SCT (autologous or syngeneic *v* allogeneic), source of stem cells (peripheral blood only or combined with bone marrow *v* bone marrow), period of study (July 1994 to June 1995, July 1995 to June 1996, and July 1996 to August 1997), and occurrence of any admission mood, anxiety, or adjustment disorder. In-hospital risk factors included the regimen-related toxicity (continuous variable), graft-versus-host disease (grades 0 to 1 *v* 2 to 4), occurrence of documented infection, veno-occlusive disease, or delirium, and occurrence of any overall mood, anxiety, or adjustment disorder.

Those variables with a marginal association ($P < .10$) or significant association ($P < .05$) with LOS in univariate linear regression analysis were entered as candidate risk factors in multivariate linear regression models. For the multivariate models, a stepwise selection method was used to select significant variables. A baseline model included as independent variables admission risk factors, and a full model evaluated the additional contribution of in-hospital risk factors to the baseline model. As higher regimen-related toxicity or presence of in-hospital complications can be associated with presence of delirium[24] or any mood, anxiety, or adjustment disorder,[7-9,24] all possible interaction terms between these variables were tested. All models were adjusted for sex and age.

To meet the assumption of normality of the linear regression model, we performed a log transformation on LOS. We obtained the estimated mean percentage increase in LOS by taking the antilog of the linear regression coefficient for each independent variable. Collinearity was assessed using variance inflation factors with standard residuals-based diagnostic procedures being used to assess model assumptions and adequacy of the model fit. Performance of the model was assessed by the adjusted explained variance (R^2). All reported *P* values are two-tailed. *P* values were considered significant if they were less than .05. No adjustment of the alpha level for multiple tests was made. Data were analyzed using SPSS version 10.0 software (SPSS, Inc, Chicago, IL).

RESULTS

Patient Characteristics

Selected sociodemographic and medical characteristics are listed in Table 1. There were no differences in age, sex, ethnicity, hematologic diagnosis, or disease status risk between the 220 patients who participated in the study and the 15 patients not evaluated because of scheduling difficulties ($P > .20$).

Table 1. Selected Sociodemographic and Medical Characteristics (N = 220)

Characteristic	No.	%
Age, years		
Mean	38.4	
Range	16-65	
Male sex	129	58.6
White	218	99.1
Married or living with partner	141	64.1
Education, years		
Median	11	
Range	4-22	
Admission Karnofsky score < 90	34	15.5
Hematologic cancer diagnosis		
Acute myelogenous leukemia	50	22.7
Acute lymphoblastic leukemia	29	13.2
Chronic myelogenous leukemia	34	15.5
Non-Hodgkin's lymphoma	46	20.9
Hodgkin's disease	19	8.6
Multiple myeloma	27	12.3
Other*	15	6.8
Time since diagnosis, months		
Median	13	
Range	3-130	
Disease risk status		
Low	86	39.1
Intermediate	33	15.0
High	101	45.9
Allogeneic SCT†	91	41.4
Peripheral-blood stem cells‡	159	72.3
Chemoradiotherapy	64	29.1
Period of study entry		
July 1994 to June 1995	75	34.1
July 1995 to June 1996	70	31.8
July 1996 to July 1997	75	34.1
In-hospital death	12	5.5
LOS for survivors, days§		
Median	20	
Range	12-75	

*Chronic lymphocytic leukemia (n = 7), myelodysplastic syndrome (n = 5), histiocytosis (n = 1), myeloproliferative syndrome (n = 1), and granulocytic sarcoma (n = 1).

†One syngeneic SCT was placed with the autologous SCT group.

‡Two patients with a combination of peripheral blood and bone marrow were included in this group.

§LOS was calculated for 208 surviving patients.

DSM-IV Psychiatric Disorders

A total of 1,062 psychiatric assessments were performed throughout the transplant process. Rates of DSM-IV psychiatric disorders by time of diagnosis and overall prevalence rates for the total sample (n = 220) are listed in Table 2. Overall prevalence rates were as follows: 22.7% (95% confidence interval [CI], 28.2% to 17.2%) for any adjustment disorder, 14.1% (95% CI, 18.7% to 9.5%) for any mood disorder, 8.2% (95% CI, 11.8% to 4.6%) for any

Table 2. Rates of DSM-IV Psychiatric Disorders by Time of Diagnosis and Overall Prevalence Rates (N = 220)

Psychiatric Disorder	Rates by Time of Diagnosis				Overall Prevalence Rate	
	Admission Prevalence		Postadmission Incidence			
	No.	%	No.	%	No.	%
Any mood disorder	19	8.6	12	3.2	31	14.1
Major depressive episode	18	8.2	9	3.2*	27	12.3
Dysthymic disorder	2	0.9	0	0	2	0.9
Corticosteroid-induced mood disorder†	0	0	3	1.4	3	1.4
Any anxiety disorder	7	3.2	12	4.5	18	8.2
Phobic disorder	4	1.8	0	0	4	1.8
Generalized anxiety disorder	4	1.8	0	0	4	1.8
Panic disorder	0	0	3	1.4‡	3	1.4
Corticosteroid-induced anxiety disorder	0	0	9	4.0	9	4.0
Any adjustment disorder	22	10.0	34	15.4	50	22.7
With depressed mood	6	2.7	10	4.5§	16	7.3
With anxiety	7	3.2‡	10	4.5	15	6.8
With mixed anxiety and depressed mood	9	4.1*§	14	6.4	19	8.6
Delirium	0	0	16	7.3	16	7.3
Any mood, anxiety, or adjustment disorder	46	20.9	54	24.5	93	42.3
Any psychiatric disorder	46	20.9	59	26.8	97	44.1

NOTE. We used modified DSM-IV criteria to diagnose a major depressive episode. Percentages do not sum up to 100% because 20 patients had more than one diagnosis, with delirium being the most common second diagnosis (12 of 20). Values are expressed as number (percentage).

*Two patients with an admission adjustment disorder evolved into a major depressive episode.

†Two with depressive features and one with manic features.

‡Two patients with an admission adjustment disorder evolved into a panic disorder.

§Two patients changed in adjustment disorder subtype.

anxiety disorder, and 7.3% (95% CI, 10.7% to 3.9%) for delirium. Overall prevalence rate for any mood, anxiety, or adjustment disorder was 42.3% (95% CI, 48.8% to 35.8%) and for any psychiatric disorder 44.1% (95% CI, 50.7% to 37.5%). Twenty patients (9.1%) met criteria for comorbid psychiatric diagnoses, with delirium the most common second diagnosis (12 of 20).

By using serial psychiatric assessments, we were able to observe a number of changes in diagnosis. Regarding adjustment disorders, we found that 11 (18.0%) of 61 patients initially receiving this diagnosis (four at hospital admission and seven during in-hospital follow-up) evolved into a major depressive episode (n = 9) or a panic disorder (n = 2) after longitudinal assessment.

Comparing autologous and allogeneic SCT, we found no significant differences in prevalence rates of delirium (6.2% *v* 8.8%, $P = .64$), any overall mood, anxiety, or adjustment disorder (38.8% *v* 47.3%, $P = .26$), or any overall psychiatric disorder (41.1% *v* 48.4%, $P = .35$).

When we compared modified and unmodified DSM-IV approaches to diagnose a major depressive episode, we found that seven patients that met modified DSM-IV criteria for a major depressive episode were diagnosed as having an adjustment disorder when applying unmodified DSM-IV criteria and that one patient that met unmodified DSM-IV criteria for a major depressive episode was diagnosed as having an adjustment disorder when applying modified DSM-IV. No other differences in psychiatric disorder rates were observed. Therefore, the overall rate of any mood, anxiety, or adjustment disorder was the same for both approaches (42.3%), with the unmodified DSM-IV approach producing a lower rate of a major depressive episode (9.5%) compared with the modified DSM-IV approach (12.3%).

Predictors of LOS for Survivors

Median LOS for all survivors was 20 days (range, 12 to 75 days). Median LOS for survivors with any overall mood disorder (n = 27), median LOS for survivors with any overall anxiety disorder (n = 18), median LOS for survivors with any overall adjustment disorder (n = 48), median LOS for survivors with delirium (n = 10), and median LOS for survivors with none of the previous psychiatric disorders (n = 118) were 26, 24, 23, 33, and 20 days, respectively. Median LOS for survivors with any overall mood, anxiety, or adjustment disorder was 23 days (range, 13 to 64 days). Of the total of 88 survivors diagnosed with any overall mood, anxiety, or adjustment disorder, 51.1%, 81.8%, 90.9%, and 97.7% were diagnosed at hospital admission, by day 0, by day +7, and by day +14, respectively. Eight of 10 patients in whom delirium was diagnosed also met criteria for any overall mood, anxiety, or adjustment disorder and

Table 3. Univariate Predictors of LOS for Survivors (n = 208)

Variable	No.	%	Estimated Increase in LOS		P
			Unadjusted %	95% CI	
Admission risk factors					
Age, years			−0.3	−0.7-0.1	.103
Mean		38.5			
Range		16-65			
Female	88	42.3	6	−4-17	.255
Karnofsky score < 90 at admission	30	14.4	13	−1-26	.079
Hematologic cancer diagnosis					
Acute lymphoblastic leukemia	27	13.0	−10	−22-4	.153
Chronic myelogenous leukemia	29	13.9	45	27-65	< .001
Non-Hodgkin's lymphoma	45	21.6	−20	−28-−10	< .001
Hodgkin's disease	18	8.7	−16	−29-0	.053
Multiple myeloma	27	13.0	−5	−18-9	.444
Other cancer diagnoses*	14	6.7	1	−19-20	.912
Disease risk status					
Intermediate risk	30	14.4	−10	−22-3	.12
High risk	97	46.6	−8	−16-2	.107
Chemoradiotherapy	147	70.7	20	8-33	.001
Allogeneic SCT	82	39.4	21	10-33	< .001
Peripheral-blood stem cells†	155	74.5	−39	−45-−34	< .001
Period of study					
July 1995 to June 1996	66	31.7	−7	−16-4	.191
July 1996 to August 1997	72	34.6	−21	−28-−13	< .001
Any admission mood, anxiety, or adjustment disorder	45	21.6	16	3-30	.015
In-hospital risk factors					
Regimen-related toxicity			10	8-13	< .001
Median		2.5			
Range		0-10			
Documented infection	69	33.2	17	6-30	.003
Veno-occlusive disease	29	13.9	28	11-47	.001
Graft-versus-host disease, grades 2-4	7	3.4	41	8-85	.012
Delirium	10	4.8	51	20-88	< .001
Any overall mood, anxiety, or adjustment disorder	88	42.3	21	10-33	< .001

NOTE. Univariate predictors were obtained by simple linear regression. LOS was log-transformed before analysis. We took the antilog of the coefficients to obtain estimated percentage increase between patients with versus without the listed condition. The comparison categories for variables with more than two categories were acute myelogenous leukemia, low risk, and July 1994 to June 1995. Coefficients for age are interpreted as increased risk per year of life and for regimen-related toxicity as increased risk per one-point score.

*The same as those in first footnote of Table 1, except for one myelodysplastic syndrome.

†Two patients with a combination of peripheral blood and bone marrow were included in this group.

only in one case did the diagnosis of delirium precede the other psychiatric disorder.

Univariate predictors of LOS are listed in Table 3. A baseline model including admission risk factors and a full model including the additional contribution of in-hospital risk factors are displayed in Table 4. The comparisons between different categories of a particular independent variable (eg, women compared with men) are adjusted for all independent variables in the multivariate model. In the baseline model, any mood, anxiety, or adjustment disorder diagnosed at hospital admission did not reach statistical significance ($P = .69$). As LOS was defined by the number of overnight stays from day of transplantation (day 0) until hospital discharge, instead of using as an admission risk factor any admission mood, anxiety, or adjustment disorder we used any mood, anxiety, or adjustment disorder diagnosed by day 0, and we obtained the same significant predictors as shown in the baseline model of Table 4, but in this analysis having any mood, anxiety, or adjustment disorder diagnosed by day 0 showed a trend for significance in its association with increased LOS (mean LOS increase, 8%; $P = .12$). In the full model, having any overall mood, anxiety, or adjustment disorder was significantly associated with increased LOS (mean LOS increase, 8%; 95% CI, 1%

Table 4. Multivariate Significant Predictors of LOS for Survivors (n = 208)

Variable	Full Model*			Baseline Model†		
	Estimated Increase in LOS			Estimated Increase in LOS		
	Adjusted %	95% CI	*P*	Adjusted %	95% CI	*P*
Admission risk factors						
Acute lymphoblastic leukemia	−13	−21-−3	.009	−12	−21-−1	.03
Chronic myelogenous leukemia	17	6-30	.003	18	5-33	.005
Non-Hodgkin's lymphoma	−8	−15-0	.04		NS	
Karnofsky score < 90 at admission	11	1-22	.025	21	9-33	< .001
Allogeneic SCT		NS		12	3-21	.006
Peripheral blood stem cells	−30	−36-−24	< .001	−34	−40-−28	< .001
July 1995 to June 1996	−17	−23-−10	< .001	−18	−24-−10	< .001
July 1996 to August 1997	−20	−26-−13	< .001	−21	−28-−14	< .001
In-hospital risk factors						
Regimen-related toxicity	6	4-8	< .001		NA	
Any overall mood, anxiety, or adjustment disorder	8	1-15	.022		NA	

NOTE. All variables that were found to be marginally or significantly associated ($P < .10$) in the univariate analysis (Table 3) were included in the multivariate linear regression analysis. A baseline model included as independent variables admission risk factors and a full model evaluated the additional contribution of in-hospital risk factors to the baseline model. All models were adjusted for sex and age. See also NOTE of Table 3.

Abbreviations: NA, data not applicable; NS, not significant.

*Adjusted $R^2 = .607$.

†Adjusted $R^2 = .536$.

to 15%; $P = .022$) and having delirium showed a close to significant association with increased LOS (mean LOS increase, 10%; $P = .05$). Interaction terms of delirium by any overall mood, anxiety, or adjustment disorder, or any of these two psychiatric variables by regimen-related toxicity or any in-hospital risk factor did not reach statistical significance. Adjusted explained variance for the baseline and full models were 54% and 61%, respectively. When we studied the impact of mood, anxiety, and adjustment disorders as separate variables on LOS, none reached statistical significance in the multivariate models (data not shown).

Year of study entry was a multivariate significant factor predicting LOS (Table 4). Median LOS was 25, 20, and 17 days, for first, second, and third years of study, respectively. Year of study was not associated with regimen-related toxicity ($P = .86$), whereas percentage of patients receiving peripheral-blood stem cells significantly increased from the first to the third year of the study (60.0%, 72.7%, and 90.3%; $P < .001$).

DISCUSSION

To our knowledge, this is the largest in-hospital study with an unselected cohort using standardized diagnostic criteria and longitudinal assessments to estimate the prevalence of psychiatric disorders in any cancer sample. In this 3-year prospective study, we found that 44.1% of patients met DSM-IV criteria for a psychiatric diagnosis; an adjustment disorder was diagnosed in 22.7%, a mood disorder in 14.1%, an anxiety disorder in 8.2%, and delirium in 7.3%. Comparison with other studies reporting psychiatric morbidity in cancer patients is difficult because of differences in research methodology.[7-9] Our overall prevalence of psychiatric morbidity is very similar to other reports.[6,32] Outside the SCT setting, Derogatis et al[32] carried out the largest study to date that used a nonbiased sample investigating psychiatric morbidity prevalence with standardized diagnostic criteria (DSM-III). In this cross-sectional multicenter study with a sample of 215 hospitalized and ambulatory patients receiving active treatment for a variety of cancer diagnoses, 47% of patients met criteria for a psychiatric disorder; compared with our prevalence rates, they reported a higher rate of adjustment disorders (32%) and lower rates of mood (6%) and anxiety disorders (2%). These differences may be because our patients were receiving a more intensive anticancer treatment, or because our prospective inpatient design allowed us to observe a development of a depressive or an anxiety disorder from an initial adjustment disorder. Because fluctuations in severity and course of depressive and anxiety symptoms are common, studies using repeated measures at multiple points in time may be an accurate reflection of the total psychiatric morbidity. In the SCT setting, Sasaki et al[6] reported that a psychiatric disorder was diagnosed in 41% of 39 allogeneic SCT patients, with adjustment disorder (23%) and mood disorder (8%) being the two most frequent diagnoses. For those studies that only describe self-report scale scores suggestive

of a clinical diagnosis during hospitalization for SCT, depression estimates ranged from 20% to 43%,[4,5,37,38] and anxiety from 20% to 33%.[4,5,39] The limiting factors in these studies were restriction of psychiatric morbidity assessment to depressive and/or anxiety symptoms, only one preadmission or admission assessment plus one[5,37-39] or two in-hospital evaluations,[4] or a small sample size (n = 44 to 74[4,37-39] and n = 120[5]).

There were no differences in rates of psychiatric disorder variables by type of SCT. As regards studies that compared autologous and allogeneic SCT patients in terms of depressive and/or anxiety symptoms during hospitalization for SCT, one study found a poorer outcome for autologous SCT patients[4] and other studies did not find significant differences.[3,5,37]

In a multivariate full model that controlled for the effects of admission and in-hospital risk factors, having any overall mood, anxiety, or adjustment disorder was associated with an 8% LOS increase ($P = .022$). In a multivariate baseline model that controlled for the effects of admission risk factors, any mood, anxiety, or adjustment disorder diagnosed by day 0 showed a trend for significance (mean LOS increase, 8%; $P = .12$). When we considered mood, anxiety, and adjustment disorders as separate diagnoses, they did not reach statistical significance in a multivariate model. However, it is possible that a significant difference was not revealed because of the small size of the groups.

As regards the studies in medical or surgical populations that adjusted for potential confounding variables, we found that psychiatric measures such as depression,[40-43] anxiety,[40,41] stress disorders (including adjustment disorders),[42] delirium,[42-46] cognitive impairment,[40,41] or any psychiatric disorder[47] significantly increased LOS. Methodologic limitations of these studies include nonuse of standardized psychiatric diagnostic criteria,[40,41] retrospective reviews from hospital discharge databases with its high risk of underdiagnosis,[42,47] restriction to an elderly sample,[43-46] and a highly biased sample.[46]

Several mechanisms underlying the association between any mood, anxiety, or adjustment disorder and increased LOS may be proposed. There is a tendency of depressive or anxiety disorders to present with multiple or unexplained physical complaints,[13,14,48,49] or to be frequently associated with pain symptoms.[15,50] This increased symptom burden can increase LOS by itself or indirectly, by leading to more extensive and time-consuming tests. It is also likely that behavioral phenomena such as noncompliance with treatment recommendation may affect the relation between depression and longer LOS.[16] Nonadherence can be manifested as a difficulty in accepting medication, nursing services, or diagnostic tests; poorly performing daily self-care behaviors needed to prevent the high risk of infection; or as a low discharge disposition. Although research on psychoneuroimmunology is still in its infancy,[8,51] accumulating evidence supports the view that psychological stress has an adverse effect on immunologic function, resulting in reduced ability to resist cancer progression[52] or difficulties in resolution of infectious episodes.[51] Another possible explanation is that a longer LOS induces psychiatric morbidity. However, most patients were diagnosed at hospital admission or initial hospitalization. Finally, it is possible that psychiatric morbidity may be an indirect indication of severity of complications or treatment-related toxicity. Nonetheless, psychiatric disorder variables remained significant after adjusting for potential confounding variables.

In the multivariate analysis, having delirium showed a close to significant association with increased LOS ($P = .05$). However, it is possible that a significant difference was not revealed because of the small number of survivor patients who had delirium (n = 10). Delirium is often difficult to diagnose and treat. Its symptoms are diverse, sometimes mistaken for mood or anxiety disorders, and the clinical findings may vary or fluctuate. The difficulty in providing good medical care, the delay in diagnosis, and the fact that delirium is often a proxy for increased medical morbidity or complications could explain the close to significant association of delirium with LOS.[24] The findings of this study are strengthened by its prospective design, good recruitment rates, large population, use of standardized psychiatric diagnostic criteria, and a comprehensive set of clinical risk variables considered for risk adjustment.

Most studies analyzing LOS or costs of SCT (considered as a proxy for LOS) have usually focused on specific treatment protocols without examining the patient characteristics and medical complications associated with these outcomes.[53-56] We have found only one prospective study in which costs of SCT were analyzed by using admission and in-hospital risk factors (not including psychiatric measures).[34]

Our finding that cancer type,[34] use of peripheral-blood stem cells,[53-56] in-hospital complications or toxicity from treatment,[34,54,56] and year of study[34,54] are significantly associated with LOS confirms the reports of others on factors associated with LOS or costs of SCT. Bennet et al[54] suggested that LOS and cost in autologous SCT decreased over time in relation to improvement in supportive care technologies, better patient selection, and experience of the transplant team. Lee et al[34] found that costs and LOS for autologous SCT decreased with time whereas costs for allogeneic SCT increased and LOS did not significantly change. However, in their study[34] only 3% of allogeneic SCT patients received peripheral-blood stem cells. In our

sample, the increasing proportion of patients receiving peripheral-blood stem cells over the course of the study could in part explain the shortening in LOS.

This study has several limitations. First, we only focused on a limited range of psychiatric conditions known to be common in cancer patients,[6-9,32] so as not to impose an undue burden on our patients. Second, although we did not measure interrater reliability, we sought to maximize the reliability of our psychiatric diagnoses by using standardized diagnostic criteria, serial observations, multiple sources of information, and discussion in regular meetings between investigators. Third, the data abstractor was not formally blinded to LOS. Although this may have influenced the results, strict guidelines were followed to rate the Bearman Toxicity Scale and clear definitions of in-hospital complications were applied. Fourth, in order to reduce the possibility of a type II error, mood, anxiety, and adjustment disorders were combined into one group. However, this composite variable was justified by the consistently higher median LOS for patients with those disorders, and by the frequent coexistence of depressive and anxiety symptoms.[7,9] Fifth, as in any single-institution study, some conclusions are specific to our center and reflect our patient characteristics and practice patterns. However, the multivariate analysis controlled for a wide range of confounding variables, and our results supported relatively robust inferences about the association of LOS with admission and in-hospital risk factors. Sixth, possible benefits from psychiatric treatment on LOS cannot be evaluated under the available design. In such a naturalistic observational sample, comparisons of outcomes on the basis of treatment received are subject to substantial bias. Seventh, we did not measure costs of care during hospitalization. In a previous study, LOS was significantly correlated with hospitalization costs for autologous and allogeneic SCT (partial $r^2 = .76$ and .77, respectively).[34] Another study reported an association between decreased LOS and lower costs.[54] Although LOS can be considered a proxy for costs, adding economic measures can give a more complete view than merely assessing hospital LOS. Finally, the cross-sectional data indicating an association between any overall mood, anxiety, or adjustment disorder and longer LOS precludes definitive causal inferences. However, when we used as a predictor variable any mood, anxiety, or adjustment disorder diagnosed by day 0, we found a trend for significance ($P = .12$), suggesting that psychiatric morbidity may have a role in predicting LOS.

In cancer populations, the effect of psychopharmacologic and psychological interventions has been reviewed and shown to be beneficial.[7-9,57] Research must focus on the development of models directed to early detection and effective treatment of psychiatric disorders. Because of our relatively high prevalence of psychiatric disorders at hospital admission, it would be better to conduct a first comprehensive assessment after the patient agrees to undergo SCT. The high prevalence of a psychiatric disorder enhances the practical utility of a screening program by increasing the positive predictive value. Furthermore, the homogeneity of the psychiatric disorders studied permits the application of specific, replicable, targeted intervention studies.[24] Adding measures of costs to the intervention studies is likely to be of more relevance to health policy than merely assessing hospital LOS. Although it remains to be determined whether early recognition and effective treatment of psychiatric disorders will result in shorter LOS or lower costs, it has the potential to improve medical practice, reduce patient suffering, enhance patient quality of life, and improve health care outcomes. Among other outcomes, the course and predictors of psychiatric disorders and their impact on quality of life and survival will be presented in future articles.

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4.5 Stem cell transplantation: risk factors for psychiatric morbidity.

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Stem cell transplantation: Risk factors for psychiatric morbidity

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ABSTRACT

The aim of this study was to determine the risk factors for psychiatric disorder in haematological cancer patients during hospitalization for stem cell transplantation. In this 3-year prospective study, 220 patients received stem cell transplantation at a single institution. Structured psychiatric interviews applying standardized diagnostic criteria were performed at hospital admission and weekly during hospitalization until discharge or death, yielding a total of 1062 interviews. Psychiatric disorder (any depressive, anxiety, or adjustment disorder) prevalence at the time of hospital admission was 21% and psychiatric disorder incidence during post-admission follow-up was 22%. After adjusting for multiple confounders in multivariate logistic regression analyses, we found that younger age, women, a past psychiatric history, lower functional status, pain, smoking cessation, and higher regimen-related toxicity were significantly associated with psychiatric disorder risk. Our study findings may help to improve identification of the patients most at risk for psychiatric disturbances during hospitalization for stem cell transplantation.

1. Introduction

Cancer is a life-threatening disease, and its psychological impact on patients has been an important aspect of clinical oncology. In most cancer patients with a positive psychiatric condition depression and/or anxiety are the central symptoms.[1–7] Methodological shortcomings in the cancer literature regarding risk factors for psychiatric disorders include retrospective or cross-sectional designs, sampling bias, only focusing on a limited number of risk factors, lack of assessment by multivariate statistical methods, or small sample size. Moreover, most of the published studies have used patient-rated depression or anxiety scale scores at a level suggestive of a clinical diagnosis, without using structured clinical interviews and/or standardized diagnostic criteria.[1–5] Clinician interviews and standardized diagnostic criteria such as the 'Diagnostic and Statistical Manual for Mental Disorders, 4th ed.' (DSM-IV[8]) or The World Health Organization International Classification of Disorders have long been held to be the gold standard for detecting psychiatric disorders.[1–5]

To the best of our knowledge only one study[6] has investigated multivariate risk factors for psychiatric disorders during hospitalization for stem cell transplantation (SCT). Sasaki and colleagues[6] diagnosed a mental disorder according

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to DSM-IV criteria in 16 (41%) of 39 allogeneic SCT patients. Higher anxiety prior to isolation, unrelated donor, and female sex predicted the occurrence of psychiatric disorders during isolation. However, their findings were limited by the small sample size and by the use of a very heterogeneous sample of psychiatric disorders for risk factor analysis.

Depression and/or anxiety may have a deleterious effect in many ways: it may impair quality of life;[9,10] increase symptom burden[2] and pain intensity;[2,4,5,11] lower compliance with medical treatment;[12] reduce overall survival time;[10] and increase health care costs[13] and hospital stay.[7] The high prevalence of depression or anxiety during hospitalization for SCT,[6,7] the associated complications mentioned above, and the fact that anxiety and depression tend to be under recognized in oncology patients[14] highlight the critical importance of identifying and treating these disorders in transplant patients.

In this 3-year prospective study carried out during hospitalization for SCT, we evaluated psychiatric disorders (depressive, anxiety, and adjustment disorders) based on structured psychiatric interviews and standardized DSM-IV diagnostic criteria. Weekly interviews were carried out from hospital admission until discharge or death. In an earlier report from our cohort,[7] we reported the general prevalence of DSM-IV psychiatric disorders and its association with a longer hospital stay. The purpose of the current paper was to identify risk factors associated with existing psychiatric disorders at the time of hospital admission or with new psychiatric disorders occurring during post-admission follow-up.

2. Patients and methods

2.1. Study population

Patients were consecutively recruited from the SCT Unit, Hospital Clínic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were haematological malignancy, at least 16 years of age, patient's first SCT, and verbal informed consent. Of 253 patients that received an SCT, 235 met the eligibility criteria. Due to scheduling difficulties, 15 patients could not be interviewed at the first assessment and were excluded from the study. All patients who were approached agreed to be interviewed. Thus, the final study cohort included 94% of the eligible population (220/235). There were no differences in age, sex, haematological diagnosis, or disease risk status between the 220 patients who participated in the study and the 15 who were excluded ($P > 0.20$).

2.2. Study procedures

Detailed information on transplant regimens, graft-versus-host disease prophylaxis and patient care has been published elsewhere.[7] Briefly, patients were assessed in a first structured interview within 48 h of hospital admission (day −9 to day −4, depending on the conditioning regimen), and subsequently on a weekly basis from day of transplant (day 0) until discharge or death (day +7; day +14; day +21 and so on). The first interview lasted 15–45 min and included sociodemographic data, assessment of past and current psychiatric status with structured interview and DSM-IV criteria, and the Nottingham Health Profile.[15] In the following weekly assessments, we administered a brief psychiatric structured interview with DSM-IV criteria lasting 5–15 min. At hospital admission a Karnofsky score[16] was obtained from the haematologist. After discharge, using a standardized form, J.M.P abstracted pertinent clinical data required to rate the regimen toxicity scale.[17] After discharge, using a standardized form, J.M.P abstracted pertinent clinical data required to rate the regimen toxicity scale.[17] For each particular patient, rating of the post-admission risk factors (regimen toxicity, graft-versus-host-disease, and documented infection) was obtained from the same in-hospital follow-up period used to rate the post-admission psychiatric disorder cases. For a patient who received the last psychiatric assessment at day +14 and was discharged on day +20, the rating of the post-admission risk factors was obtained from the period between the start of the conditioning regimen and day +14.

2.3. Psychiatric assessment

Three interviewers participated in the study: two psychiatrists (J.M.P. and J.B.) and a 4th year psychiatric resident (J.A.). Psychiatric information from the patient interviews was complemented with information from the family and medical and nursing staff. Psychiatric diagnoses were assigned at a diagnosis meeting held every two months, at which a consensus diagnosis was reached on each patient. No interrater reliability assessment was carried out.

2.3.1. Current psychiatric status

A complete description of the psychiatric assessment has been published elsewhere.[7] Briefly, the psychiatric interview followed a structured format with psychiatric diagnoses being defined according to DSM-IV criteria. Our aim was to conduct a relatively short psychiatric interview focusing on depressive, anxiety, and adjustment disorders known to be common in cancer patients.[1–5] The alterations in some depressive symptoms such as anorexia, and fatigue as a direct result of the neoplastic process or cytotoxic treatment present a methodological problem for the diagnosis of depression in cancer patients.[2,3,9,18] In our study setting, in which intensive conditioning treatment is used, most of the patients present fatigue and anorexia. The DSM-IV requires a symptom to be counted toward the diagnosis of depression only if it is thought not to be due to cancer or its treatment, with a consequent risk for under diagnosis in the SCT setting. As in our previous report,[7] we used the model of the Sloan-Kettering Cancer Institution group to diagnose major depression. For research purposes, this method is the best of the four possible diagnostic models available, as it maximizes specificity.[18] It ensures the most homogeneous depressed group possible, with the fewest confounding variables, thereby increasing the clinical and statistical significance of the research data.[18] The Sloan-Kettering method eliminates anorexia and fatigue from the list of nine major depression criteria, and requires only four (instead of five) of the remaining seven symptoms for diagnosis.

2.3.2. Psychiatric rates by time of diagnosis and overall prevalence rates

Depending on the time of psychiatric diagnosis, we made a distinction between admission prevalence and post-admis-

sion incidence. Admission prevalence is the rate at which existing disorders are diagnosed at hospital admission (first interview). Post-admission incidence is the rate with which new disorders occur during in-hospital follow-up (from the second interview until discharge or death). Post-admission incidence rates were calculated for patients with no psychiatric disorder at the time of hospital admission. Overall prevalence is the rate at which existing disorders are diagnosed during the hospitalization period (from hospital admission until discharge or death).

2.4. Instruments

2.4.1. Functional status

The Karnofsky Performance Scale[16] is an index of physical disability developed for the evaluation of oncology patients. Lower scores reflect greater impairment in normal activity, work, and self-care.

2.4.2. Nottingham health profile

This self-administered questionnaire contains 38 statements belonging to six dimensions of health: physical mobility, energy, pain, sleep, social isolation, and emotional reactions. Higher scores indicate more health problems. The reliability and validity of this scale have been demonstrated elsewhere.[15] In our investigation we used the validated Spanish version.[19] We planned the pain and social subscales to be used as risk factors for depression and anxiety. Cronbach's alphas for those pain and social isolation subscales measured at hospital admission were 0.77 and 0.34, respectively. Since the internal consistency of the social subscale was unacceptably low it was discarded to be used in statistical analysis.

2.4.3. Regimen-related toxicity

The Bearman Toxicity Scale[17] is used to specifically rate the complications due to chemotherapy or chemoradiotherapy during hospitalization for SCT, with higher scores reflecting higher toxicity.

2.5. Other study variables

2.5.1. Smoking cessation

Smoking cessation was defined as reporting active smoking within one month of hospital admission, since the onset of depressive or anxiety symptoms can range from 2 days up to several weeks after the initial abstinence from smoking.[8,20]

2.5.2. Alcohol intake

According to the units of alcohol consumption per week (1 unit = 8 g of alcohol), patients were subdivided into three groups:[21] low risk, hazardous, and dangerous. In our study we compared dangerous intake versus other categories since dangerous consumption is more likely to be associated with mental problems.[21]

2.6. Statistical analysis

Because of the frequent coexistence of depressive and anxiety symptoms,[3,4,6,7] the tendency in the hospital SCT setting for adjustment disorders to develop into specific depressive or anxiety disorders,[7] and our aim to increase sample size in order to reduce the possibility of a type II error, we pooled the depressive, anxiety, and adjustment disorders into a composite psychiatric disorder variable. Each patient was placed in one of two groups, according to their diagnosis of depressive, anxiety, or adjustment disorder. If patients were not diagnosed with either, then they were categorized in the no psychiatric disorder group. If they were diagnosed with either of them, then they were categorized in the psychiatric disorder group. In order to better delineate the risk factors associated with depression or anxiety, patients meeting criteria only for corticosteroid-induced depressive disorder ($n = 1$) or corticosteroid-induced anxiety disorder ($n = 6$) were either excluded from the statistical analysis or included in the "no psychiatric disorder" group. As the same significant factors were found in all multivariate models using either method, in our presentation of the results the corticosteroid-induced disorders are included in the "no psychiatric disorder" group.

Univariate and multivariate logistic regression analysis was used to identify risk factors for psychiatric disorder. Admission and post-admission risk factors used to predict psychiatric disorder were chosen based on past work in the field and due to their clinical relevance.[1,2,4] Admission risk factors included age (continuous variable), sex (male versus female), marital status (married/cohabitating versus not married/not cohabitating), living alone (no versus yes), education (continuous), past psychiatric history (no versus yes), smoking cessation (no active smoker versus stop smoking), alcohol intake (low risk and hazardous versus dangerous), score for pain on the Nottingham Health Profile (0 versus >0), Karnofsky score (90–100 versus <90), disease risk status (low, intermediate, and high), type of SCT (autologous or syngeneic versus allogeneic), and conditioning regimen (chemotherapy only versus chemoradiotherapy). Post-admission risk factors included regimen-related toxicity score (continuous), graft-versus-host disease (grades 0–1 versus 2–4), and occurrence of documented infection (no versus yes). We dichotomized the pain and Karnofsky scores because their distributions were highly skewed.

The results of the logistic regression are reported as odds ratios (ORs) with 95% confidence interval (CIs). Variables having a P-value <0.20 in univariate logistic regression analysis were entered as candidate risk factors in multivariate logistic regression models. In multivariate logistic analysis, we used a backwards stepwise regression process using the likelihood ratio test. Patients with a missing value on any scale were omitted from statistical analyses. All reported P-values were two-tailed. P-values were considered significant if they were less than 0.05. For this exploratory study, no adjustment of the alpha level for multiple tests was made. Data were analyzed using SPSS version 11.5 software (SPSS Inc., Chicago, IL).

3. Results

A total of 1062 psychiatric interviews were performed from hospital admission to discharge or death. Rates of specific DSM-IV psychiatric disorders by time of diagnosis and overall prevalence rates for the total sample ($n = 220$) are presented in

Table 1 – Rates of DSM-IV psychiatric disorders

Psychiatric disorder	Rates by time of diagnosis		Overall prevalence rates (n = 220)
	Admission prevalence (n = 220)	Post-admission incidence (n = 174)	
Any depressive disorder	19 (9)	7 (4)	28 (13)
Major depression	18 (8)	7 (4)	27 (12)[a]
Dysthymia	2 (1)	0 (0)	2 (1)
Any anxiety disorder	7 (3)	1 (1)	10 (5)
Phobia	4 (2)	0 (0)	4 (2)
Generalized anxiety disorder	4 (2)	0 (0)	4 (2)
Panic disorder	0 (0)	1 (1)	3 (1)[b]
Any adjustment disorder	22 (10)	32 (18)	50 (23)
With depressed mood	6 (3)	8 (5)	16 (7)[c]
With anxiety	7 (3)[b]	10 (6)	15 (7)
With mixed anxiety and depressed mood	9 (4)[a,c]	14 (8)	19 (9)
Any psychiatric disorder	46 (21)	39 (22)	85 (39)

Percentages do not add up to 100% because five patients had more than one diagnosis. Values are expressed as number (percentage). Incidence rates were calculated for patients with no psychiatric disorder at admission. DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, 4th ed.

a Two patients with an admission adjustment disorder evolved into a major depression.

b Two patients with an admission adjustment disorder evolved into a panic disorder.

c Two patients changed in adjustment disorder subtype.

Table 1. At hospital admission, we found 46 out of 220 (21%) patients meeting criteria for any psychiatric disorder (including any depressive, anxiety, or adjustment disorder). During post-admission follow-up 39 out of 174 (22%) patients developed new disorders meeting criteria for any psychiatric disorder. Of these post-admission psychiatric disorders, 85% (34/40) were diagnosed in the first two weeks after hospital admission.

Three multivariate logistic models were carried out: one to predict admission psychiatric disorder and two to predict post-admission psychiatric disorder. Three multivariate logistic models were carried out: one to predict admission psychiatric disorder and two to predict post-admission psychiatric disorder. An admission psychiatric disorder model included as independent variables all admission risk factors. A baseline post-admission psychiatric disorder model included as independent variables all admission risk factors and a full post-admission model, evaluated the additional contribution of post-admission risk factors to the baseline model. In the admission model, all patients were used for statistical analysis, whereas patients with a psychiatric disorder at the time of hospital admission were not included in the post-admission models. Table 2 shows the univariate predictors of psychiatric disorder by time of diagnosis.

Multivariate predictors of admission and post-admission psychiatric disorder are displayed in Table 3. A past psychiatric history and lower functional status were significantly associated with admission psychiatric disorder. In the baseline model predicting post-admission psychiatric disorder, younger age, presence of pain, a past psychiatric history, and smoking cessation emerged as multivariate risk factors. In the full model, post-admission psychiatric disorder was significantly associated with presence of pain, a past psychiatric history, smoking cessation, and higher regimen-related toxicity, with younger age showing a close to significant association (P = 0.056).

4. Discussion

The current report yields several findings regarding risk factors for psychiatric disorder during hospitalization for SCT. Given the paucity of data concerning risk factors associated with psychiatric disorders in the SCT setting,[6] we compared our results with studies in the general cancer literature analysing multivariate risk factors for depression, anxiety, or a global psychiatric measure including both depression and anxiety.

In our study, presence of a past psychiatric history was associated with an admission psychiatric disorder and also predicted subsequent psychiatric disorders during post-admission follow-up. A past psychiatric history may indicate patient vulnerability to develop a psychiatric disorder when confronted with a stressful environment. Many studies in the cancer literature have consistently reported an association between a past psychiatric history and depression[11,22–26] or anxiety.[23,24]

Research has shown that mental health declines along with physical status.[1–5] In accordance with these data, we found that higher regimen-related toxicity, lower functional status, and pain were significantly associated with psychiatric morbidity. Mini-transplants use moderately high-dose chemotherapy, appearing to be a safer and less toxic alternative to conventional allogeneic SCT. With the use of mini-transplant nowadays, we would expect a lower incidence of post-admission psychiatric morbidity. Studies should be performed to determine more precisely the psychiatric impact of this new transplant technique. Several cancer studies have reported a significant association between lower functional

Table 2 – Univariate predictors of psychiatric disorder by time of diagnosis

	Total sample (n = 220)	No psychiatric disorder (n = 135)	Psychiatric disorder			
			Admission cases (n = 46)	Admission models (n = 220)	Post-admission cases (n = 39)	Post-admission models (n = 174)
	Value	Value	Value	OR (95% CI)	Value	OR (95% CI)
Admission risk factors						
Age, years	38.0 (16–65)	40.0	39.5	1.00 (0.97–1.02)	36.0	0.98 (0.95–1.01)*
Female	91 (41)	37	39	0.89 (0.46–1.73)	59	2.44 (1.18–5.06)**
Not married	79 (36)	35	37	1.06 (0.54–2.08)	39	1.17 (0.56–2.44)
Living alone	9 (4)	4	7	1.95 (0.47–8.13)	3	0.68 (0.08–6.04)
Education, years	11.0 (4–22)	11.0	10.0	0.96 (0.89–1.04)	11.0	0.96 (0.88–1.05)
Past psychiatric history	84 (38)	26	67	4.71 (2.35–9.46)***	46	2.45 (1.17–5.12)**
Smoking cessation	41 (19)	15	24	1.51 (0.69–3.30)	26	1.98 (0.84–4.69)*
Dangerous alcohol intake	14 (6)	7	7	1.03 (0.28–3.87)	3	0.33 (0.04–2.65)
Pain score > 0	71 (34)	27	48	2.09 (1.05–4.15)**	42	1.97 (0.93–4.19)*
Karnofsky score < 90	34 (15)	11	28	2.87 (1.31–6.31)***	15	1.46 (0.52–4.04)
Disease risk status						
Intermediate risk	33 (15)	15	17	1.51 (0.57–4.00)	13	1.02 (0.33–3.19)
High risk	101 (46)	43	50	1.40 (0.68–2.88)	51	1.40 (0.65–3.05)
Allogeneic SCT	91 (41)	40	39	0.89 (0.46–1.73)	49	1.43 (0.70–2.92)
Chemoradiotherapy	156 (71)	69	74	1.21 (0.58–2.52)	74	1.31 (0.59–2.93)
Post-admission risk factors						
Regimen toxicity score	3.0 (0–10)	2.0			3.0	1.35 (1.12–1.64)***
GVHD, grades 2–4	10 (5)	3			13	4.82 (1.23–18.91)**
Documented infection	75 (34)	30			33	1.19 (0.56–2.54)

For the total sample column, values are reported as number (%) except for age, education, and regimen toxicity that are expressed as median (range). In all other columns values are expressed as % or median. Missing data: pain score, n = 10. GVHD, graft-versus-host disease; OR, odds ratio; 95% CI, 95% confidence interval. Levels of significance: *P < 0.20, **P < 0.05, ***P < 0.01.

Table 3 – Multivariate predictors of psychiatric disorder by time of diagnosis

	Admission psychiatric disorder model[a]		Post-admission psychiatric disorder			
			Baseline model[b]		Full model[c]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Admission risk factors						
Age	–	–	0.97 (0.94–1.00)	0.049		0.056
Female	–	–	2.50 (1.13–5.52)	0.024	2.41 (1.07–5.47)	0.035
Past psychiatric history	6.21 (2.87–13.43)	<0.001	2.34 (1.05–5.23)	0.039	2.49 (1.09-5.72)	0.031
Smoking cessation	–	–	2.57 (1.01–6.56)	0.048	2.95 (1.12–7.76)	0.029
Pain score > 0		0.12	2.33 (1.03–5.26)	0.042	2.33 (1.01–5.38)	0.049
Karnofsky score < 90	3.07 (1.23–7.67)	0.016	–	–	–	–
Post-admission risk factors						
Regimen-related toxicity	–	–	–	–	1.36 (1.11–1.67)	0.003
GVHD, grades 2–4	–	–	–	–		0.48

Variables with a P value <0.20 in univariate analysis (Table 2) were included in multivariate regression models. An admission psychiatric disorder model included admission risk factors as independent variables. A baseline post-admission psychiatric disorder model included admission risk factors as independent variables and a full model evaluated the additional contribution of post-admission risk factors to the baseline model. Due to missing data on the pain score: 10 patients were missing on the admission model and 6 patients on each of the post-admission models. GVHD, graft-versus-host disease; OR, odds ratio; 95% CI, 95% confidence interval.

a n = 210. Summary statistics: model χ^2 = 29.09, P < 0.001; goodness of fit, P = 0.87.

b n = 168. Summary statistics: model χ^2 = 19.40, P = 0.002; goodness of fit, P = 0.69.

c n = 168. Summary statistics: model χ^2 = 28.58, P < 0.001; goodness of fit, P = 0.51.

status and depression,[23–25] anxiety,[25] or an overall psychiatric disorder variable including major depression and adjustment disorders.[27] A substantial body of research suggests a relationship between pain and depression and/or anxiety, but the cause-and-effect nature of the association remains unclear.[4,5,11,26] Although our results provide support for the

prognostic importance of pain, they do not establish that pain causes psychiatric morbidity. To establish a causal relationship, we need longitudinal research combining repeated measurement of psychiatric disorders and its presumed pathophysiological mechanisms, followed by adequately powered, randomized trials targeting the implicated mechanisms. Our finding of a significant association between pain and psychiatric morbidity suggests the potential importance of the physician's role in reducing depression and/or anxiety through pain management, because pain is a factor that physicians can impact.

Another noteworthy finding in this study was that smoking cessation at the time of hospital admission was significantly predictive of a psychiatric disorder occurring during post-admission follow-up, even after adjusting for potential in-hospital confounding variables. The combination of case reports of cessation-associated severe depressions that can often be reversed by smoking, the need for sustained antidepressant treatment in some abstinent smokers, and the disproportionate development of depressive and anxiety symptoms during withdrawal among some smokers[8,20] reinforces the observation that cancer patients who smoke are at risk for psychiatric morbidity when they enter a medical care setting in which smoking restrictions are applied. Smoking cessation services early in the disease process may have a role in promoting physical and psychological health.

In line with our data, several oncological investigations have reported a significant association between female sex and anxiety[9,24,28] or depression.[28] Our data also corresponded with the large epidemiological studies linking female gender and higher rates of psychiatric morbidity.[29,30] Our finding of a significant association between younger age and depression and/or anxiety, is consistent with the results of previous cancer studies.[11,22,25,31] In younger patients compared to their older counterparts, anticancer treatment can lead to infertility, the entire disease and treatment process can represent a much greater loss of their role in the family, occupational and social activity, which overall may have a negative effect on their emotional status.

This study has several limitations. First, we only focused on a limited range of psychiatric conditions known to be common in cancer patients, [1–6] so as not to impose an undue burden on our patients. Second, although we did not measure interrater reliability, we sought to maximize the reliability of our psychiatric diagnoses by using standardized diagnostic criteria, serial observations, multiple sources of information, and discussion in regular meetings between investigators. Third, the use of only one data abstractor to rate the regimen-related toxicity scale represents another design limitation. However, strict guidelines were followed to rate the Bearman Toxicity Scale and clear definitions of in-hospital complications were applied. Fourth, due to the low Cronbach's alpha for the social isolation subscale we could not study the effect of perceived social support. Further research is needed on more sensitive social support measures to explore their role in predicting depression or anxiety. Finally, there are threats to generalizability in a study from a single institution. However, the findings of this study are strengthened by high recruitment rates, large population, and a comprehensive set of clinical risk variables considered for risk adjustment. Moreover, the use of a rigorous diagnostic method (structured psychiatric interview applying standardized diagnostic criteria) coupled with serial psychiatric evaluations during hospitalization for SCT (1062 psychiatric assessments were performed throughout the transplant process) may give a more accurate reflection of the psychiatric morbidity.

The risk factors examined in the current paper are mostly non-modifiable, a fact that limits the possibility of introducing successful prevention strategies. However, our study findings have clinical implications for physicians seeking to improve identification of patients most at risk for psychiatric disturbances during hospitalization for SCT. Because of our relatively high prevalence of psychiatric morbidity at hospital admission, it would be better to conduct first a comprehensive assessment after the patient agrees to undergo SCT, complemented by brief interviews during hospitalization for SCT. Although it remains to be determined whether early recognition and effective treatment of emotional deficits during the hospitalization period will result in better transplant outcomes, it has the potential to improve medical practice, reduce patient suffering, and enhance quality of life.[2,4,5,7,9–13]

Conflict of interest statement

There is no any financial or personal relationship with other people or organisations that could inappropriately influence or bias the authors' work.

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4.6 Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation.

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ORIGINAL REPORT

Role of Depression As a Predictor of Mortality Among Cancer Patients After Stem-Cell Transplantation

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ABSTRACT

Purpose
To determine the association between depression and survival among cancer patients at 1, 3, and 5 years after stem-cell transplantation (SCT).

Patients and Methods
This was a prospective cohort study of 199 hematologic cancer patients who survived longer than 90 days after SCT and who were recruited in a University-based hospital between July 1994 and August 1997. Patients received a psychiatric assessment at four consecutive time points during hospitalization for SCT, yielding a total of 781 interviews. Depression diagnoses were determined on the basis of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Results
Eighteen (9.0%) and 17 patients (8.5%) met criteria for major and minor depression, respectively. Multivariate Cox regression models found major depression to be predictive of higher 1-year (hazard ratio [HR], 2.59; 95% CI, 1.21 to 5.53; $P = .014$) and 3-year mortality (HR, 2.04; 95% CI, 1.03 to 4.02; $P = .041$) but not 5-year mortality (HR, 1.48; 95% CI, 0.76 to 2.87; $P = .249$). Minor depression had no effect on any mortality outcome. Other multivariate significant predictors of higher mortality were higher regimen toxicity in the 1-, 3-, and 5-year models; older age and acute lymphoblastic leukemia in the 3- and 5-year models; chronic myelogenous leukemia in the 3-year model; and lower functional status and intermediate/higher risk status in the 5-year model. Use of peripheral-blood stem cells predicted lower mortality in the 5-year model.

Conclusion
After adjusting for multiple factors, major depression predicted higher 1- and 3-year mortality among cancer patients after SCT, underscoring the importance of adequate diagnosis and treatment of major depression.

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INTRODUCTION

Depression, which is defined by a wide variety of measures, has been associated with higher rates of mortality in a number of different clinical and community samples.[1-13] This association has been best established in patients with cardiovascular disease.[1-4] The question as to whether depression influences survival among patients with cancer has also been the subject of many research studies. Although the literature on this issue is divided, most authors suggest a connection.[9-13] In a recent literature review of 24 published studies, 15 reported positive associations between depression and cancer progression or mortality.[9]

Methodologic shortcomings in the cancer survival literature include retrospective designs, sampling bias, small sample size, the use of only one-time measurement of depression, and inadequate appraisal of the

complex interrelations between depression and other predictors of death.[4,9] Moreover, most of the studies published have defined depression by using different patient-rated depression scale scores at a level suggestive of a clinical diagnosis, without using structured clinical interviews and/or standardized diagnostic criteria.[4,9] In contrast with depression as defined by standardized diagnostic criteria that take into account the overall time course of depressive symptoms to diagnose a depressive episode, patient-rated depression scales are limited by their ability to only assess depressive symptomatology within the last week of evaluation, with a consequent risk of misclassifying persons as depressed as a result of stressful life circumstances or health problems present at that moment.

Hematopoietic stem-cell transplantation (SCT) represents a highly aggressive and demanding medical therapy that has a profound impact at a physical and psychological level.[14,15] It is associated with severely toxic side effects, invasive medical procedures, frequent medical complications, and the risk of mortality from the procedure itself. Regarding studies on survival after SCT, only one prospective investigation with more than 100 patients examined the relationship between depression and mortality.[12] With a sample of 193 patients, Loberiza et al[12] found that depression was predictive of earlier mortality (between 6 and 12 months after SCT) but not later mortality (between 13 and 42 months after SCT). However, this study was limited because it used a nonvalidated measure of depression (a checklist of depression symptoms created by the authors) and measured depression only at 6 months after SCT. In a recent study of a sample of 72 patients, Akaho et al[16] found that a psychological variable (a mixture of depression, anxiety, anger, fatigue, and confusion) evaluated 2 weeks before SCT was predictive of earlier mortality (between 3 and 8 months after SCT) but not later mortality (between 1 and 3 years after SCT). Oncologic studies investigating the impact of depression on survival may present contradictory results because of, in part, the length of the follow-up period.[9] As survival time is extended, other intervening factors are more likely to account for mortality, thereby obscuring any possible relationship between depression and mortality.[9] Most deaths after SCT occur within the first 3 years of the intervention, and the most acute reduction of the survival rates is observed within a period of 12 to 24 months after transplantation.[17] Therefore, we considered it to be clinically relevant to study risk factors for short-, intermediate-, and long-term mortality after SCT. Specifically, the purpose of the current article was to study the effect of depression on 1-, 3-, and 5-year mortality after SCT. We evaluated depression with standardized diagnostic criteria (Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition[18] [DSM-IV]) at four consecutive time points during hospitalization for SCT. Because depression is common in patients with cancer,[9,19,20] an association between depression and mortality would be of significant clinical importance. Effective treatment for depression is available; therefore, early recognition of the condition and adequate treatment could improve medical outcomes, such as survival after SCT.

PATIENTS AND METHODS

Patients

The methods used have been described in detail elsewhere.[15] Briefly, patients were consecutively recruited from the SCT Unit, Hospital Clinic, Barcelona, between July 21, 1994, and August 8, 1997. Inclusion criteria were hematologic malignancy, an age of at least 16 years, no prior SCT, and verbal informed consent. In the current study and because of our intention to analyze the effect of the more prevalent DSM-IV depression groups (ie, major and minor depression), we excluded from analyses the only patient who was diagnosed with dysthymia not comorbid with major depression.

Procedures

As part of the pretransplantation assessment protocol, hematologists first informed their patients about the study evaluation of quality of life and psychosocial aspects related to SCT. On their admission to the transplantation unit, the research psychiatrist gave detailed information about the protocol design, objectives, and applicability of the study. Depression interviews were carried out at hospital admission and, subsequently, on a weekly basis from day of SCT (day 0) until discharge or death (days +7, +14, +21, and so on). To limit the number of dropouts (mainly as a result of hospital discharge), we used only medical and depression data from the hospital admission interview until the day +14 interview. At hospital admission, a Karnofsky performance status score[21] was obtained from the hematologist. This scale is an index of physical disability developed for the evaluation of oncology patients, in which lower scores reflect greater impairment. After discharge, using a standardized form, the first author (J.M.P) abstracted medical diagnoses, laboratory results, vital signs, psychotropic treatment, and pertinent clinical data required to rate the Bearman Regimen Toxicity Scale[22] and also reviewed medical and nursing records to compile all written information that might relate to the patient's psychological status during hospitalization. The data abstractor was formally blinded to the survival time of each patient. The Bearman Regimen Toxicity Scale is used to specifically rate the complications caused by chemotherapy or chemoradiotherapy during hospitalization for SCT, with higher scores reflecting higher toxicity. We derived mortality data by searching medical records and making follow-up calls. All reported deaths were verified by the patient's hematologist.

Psychopharmacologic treatments were prescribed either by the corresponding hematologist or by the research psychiatrist. Psychiatric intervention (pharmacologic treatment and/or brief psychotherapeutic sessions) could be prompted by referral by the hematologist or by decision of the research psychiatrist in accordance with the hematologist. No attempt was made to influence the amount or type of psychiatric therapy administered to patients. The clinical research protocol was reviewed and approved by the Department of Psychiatry's Committee on Clinical Research.

Depression Assessment

In a checklist format, the criterion items required for the DSM-IV depressive disorders were rated during the interview by the clinician as absent, subthreshold, or present during the past week. The alterations in some depressive symptoms, such as anorexia and fatigue, as a direct result of the neoplastic process or cytotoxic treatment present a methodologic problem for the diagnosis of depression in cancer patients.[9,19,20,23] Strict or unmodified DSM-IV criteria require a symptom to be counted toward the diagnosis of depression only if it is thought not to be caused by cancer or its treatment, with a consequent risk for underdiagnosis in the SCT setting. In our study population, the percentages of patients with the DSM-IV criterion item for loss of appetite rated as present at the time of hospital admission and at the following three weekly evaluations were 30.9%, 76.9%, 88.3%, and 85.1%, respectively, whereas for the DSM-IV fatigue criterion, these figures were 30.9%, 76.9%, 88.3%, and 85.1%, respectively (unpublished data). As in our previous report,[15] we used a modified DSM-IV approach to diagnose major depression. For research purposes, the Memorial Sloan-Kettering Cancer Center (MSKCC) –modified DSM-IV approach is the best of the four possible diagnostic models available because it maximizes specificity.[23] It ensures the most homogeneous depressed group possible, with the fewest confounding variables, thereby increasing the clinical and statistical significance of the research data.[23] The MSKCC method eliminates anorexia and fatigue from the list of nine major depression criteria and requires only four (instead of five) of the remaining seven symptoms for diagnosis. To diagnose minor depression, we required two or three out of the seven symptoms in the MSKCC method. For diagnosis of a major or minor depression, the minimum required symptom criteria had to persist for most of the day, nearly every day, for at least 2 consecutive weeks (temporal criterion). If, in a particular weekly interview, a patient met symptom criteria for major depression and, in the following interview, met symptom criteria for minor depression, a diagnosis of minor depression was established. If, at the following interview, this patient did not meet criteria for any depression, the diagnosis was no depression. An episode of major depression may fluctuate in symptom severity over time. At the time of the first hospital interview, we explored the presence of a major or minor depressive episode during the previous weeks before hospital admission. A major depressive episode in partial remission was diagnosed when symptoms of a major depressive episode had been present during the previous weeks but minimum symptom criteria were not met at the time of the interview or there was a period without any significant symptoms of a major depressive episode lasting less than 2 months after the end of the major depressive episode.[18] In accordance with DSM-IV criteria, patients with minor depressive episodes in partial remission were considered as having no depression. For the purposes of the present study, each patient was placed in one of the following three groups: no depression, minor depression (only current criteria), and major depression (whether currently meeting criteria or in partial remission).

Three interviewers participated in the study; the main investigator was a psychiatrist (J.M.P.), and the two other interviewers were a fourth-year psychiatric resident (J.A.) who participated in the study for the first 11 months and a psychiatrist (J.B.) who participated in the rest of the study. Each patient was interviewed by only one of the interviewers. Consensus diagnostic meetings were held every 2 months. At the meetings, the corresponding psychiatric interviewer reported the patient's psychological status from multiple data sources, including all weekly DSM-IV depression checklists, additional information from direct interviews (appearance, facial expression, attitude, and degree of collaboration), past personal and family psychiatric history obtained from the patient, opinions of the doctor and nurse responsible for the patient during hospitalization, opinions of the family regarding the past and current psychological status, and information from medical and nursing records regarding the medical and psychological status. The clinical presentation of each patient was meticulously reviewed in relation to the presence or absence of depressive symptoms on the DSM-IV depression checklists. After reviewing and discussing all available clinical data, diagnoses of depression were decided by consensus of two psychiatric interviewers (J.M.P. and J.A. or J.B.) with strict observance of the DSM-IV criteria. No inter-rater reliability assessment was carried out.

Statistical Analysis

To avoid mixing the acute risk of death associated with the transplantation procedure with the relation that may exist between depression and mortality, our primary analysis was performed in patients surviving longer than 90 days after SCT. The analysis was also performed in patients surviving longer than 30 days after SCT. Univariate and multivariate Cox proportional hazards models were used to determine the effect of independent predictors on survival times. Separate Cox models for 1-, 3-, and 5-year mortality were used to analyze the short-, immediate-, and long-term effects of depression on mortality after SCT. Survival time was measured in days from the date of SCT (day 0) to the date of cancer- or transplantation-related death or was censored at the corresponding 1-, 3-, or 5-year point after SCT. For the 1-year mortality model, all patients who were alive at 1 year were censored, including patients who died in years 2 to 5 after SCT. The 3- and 5-year mortality models were not conditional on living 1 and 3 years, respectively. For the 3- and 5-year mortality models, we analyzed the same sample of patients used for the 1-year mortality model, except that patients who were alive at 3 years were considered as censored in the 3-year mortality model and patients alive at 5 years were considered as censored in the 5-year mortality model. Baseline variables used as potential predictors were chosen a priori based on past work in the field and because of their clinical relevance.[4,9,12,19,20] We also included a variable encoding the year of study entry as an adjustment for practice variations. Risk factors evaluated at the time of hospital admission included age (continuous variable), sex, marital status (married or cohabitating v other), education (< 8 v > 8 years), admission Karnofsky score (90 to 100 $v < 90$), hematologic cancer diagnosis (acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and other), disease risk status (low, intermediate, and high),[24] conditioning regimen (chemotherapy v chemoradiotherapy), type of SCT (autologous or syngeneic v allogeneic), source of stem cells (peripheral blood only or combined with bone marrow v bone marrow), smoking history (yes v no), dangerous alcohol intake (yes v no),[25] and period of study entry (July 1994 to June 1995, July 1995 to June 1996, and July 1996 to August 1997). Risk factors evaluated from hospital admission until day +14 after SCT included DSM-IV depression diagnosis (no, minor, and major depression), regimen toxicity score (continuous variable), graft-versus-host disease (grades 0 to 1 v 2 to 4), and documented infection (yes v no). We dichotomized, at a clinically relevant point, the Karnofsky score because its distribution was highly skewed.

All risk factors (except for the depression variable) with $P < .20$ in univariate analysis were included in a single multivariate model. The factors found to be significant in this single multivariate model plus a term for the depression variable were all included in a final multivariate model. Because age, sex, disease risk status, Karnofsky performance status, and regimen toxicity can be associated with depression,[4,9,19,20] all possible interaction terms between depression and these variables were tested in the final multivariate models. The proportional hazards assumption for all variables was examined using interactions between covariates and time and also by inspection of log minus log curves. Construction of time-dependent covariates was used whenever nonproportional variables were identified. Because of potentially unmeasured clinical variables associated with type of SCT and because there is an intrinsic difference in the risk of death,[12] all univariate and multivariate models were stratified according to type of SCT. No information was missing for any of the predictor variables. For this exploratory study, no adjustment of the alpha level for multiple tests was made. Statistical analyses were performed using the Statistical Package for the Social Sciences version 11.5 (SPSS Inc, Cary, NC).

RESULTS

Of 253 patients who received a SCT during the 3-year recruitment period, 234 met the eligibility criteria. Because of scheduling difficulties, 15 patients could not be interviewed at the first assessment and were excluded from the study. All patients who were approached agreed to be interviewed. Thus, the study cohort included 93.6% of the eligible population (219 of 234 patients). There were no differences in age, sex, hematologic diagnosis, or disease risk status between the 219 patients who participated in the study and the 15 patients who were excluded ($P > .20$). Among these 219 patients, 199 (90.9%) survived longer than 90 days after SCT. A total of 781 (98.1%) of 796 possible psychiatric assessments with DSM-IV were conducted at four consecutive time points from hospital admission to day +14 (199, 198, 197, and 187 assessments at the four time points). Missing observations were a result of compromised medical status (one at day 0, two at day +7, and four at day +14) or a result of scheduling difficulties (five at day +14). Attrition was a result of hospital discharge (three patients were discharged by the day +14 interview). Complete 5-year follow-up data were obtained for all patients except one, who was censored at the time of last hospital contact. Only one patient died from a cause (suicide) other than a cancer- or transplantation-related death and was censored at the time of death.

Table 1 lists the baseline characteristics of patients surviving longer than 90 days after SCT. Of these 199 patients, 18 (9.0%), 17 (8.5%), and 164 (82.5%) met modified DSM-IV criteria for major, minor, and no depression during hospitalization, respectively. Of the 18 patients with major depression, seven patients currently met diagnostic criteria, and 11 were in partial remission. Of the 17 patients with minor depression, six met symptom criteria for major depression on at least one occasion during hospitalization but not the temporal criterion of 2 consecutive weeks with major depression symptomatology. Of these patients with major and minor depressive episodes, 88.9% (16 of 18 patients) and 52.9% (nine of 17 patients) were diagnosed at the time of hospital admission. The median duration time from episode onset until day +14 after SCT was 45.5 weeks (range, 3 to 163 weeks) and 6.0 weeks (range 2 to 33 weeks)

Table 1. Characteristics of Patients Surviving Longer Than 90 Days After SCT (N = 199)

Characteristic	No. of Patients	%
Age, years		
Median	39	
Range	16-69	
Female	83	41.7
Married or living with partner	127	63.8
Education > 8 years	144	72.4
Admission Karnofsky score < 90	25	12.6
Hematologic cancer diagnosis		
Acute myelogenous leukemia	45	22.6
Acute lymphoblastic leukemia	26	13.1
Chronic myelogenous leukemia	28	14.1
Non-Hodgkin's lymphoma	42	21.1
Hodgkin's disease	18	9.0
Multiple myeloma	26	13.1
Other diagnoses*	14	7.0
Disease risk status		
Low risk	79	39.7
Intermediate risk	29	14.6
High risk	91	45.7
Autologous SCT†	120	60.3
Peripheral-blood stem cells‡	148	74.4
Chemoradiotherapy	141	70.9
Smoking history	97	48.7
Dangerous alcohol intake	12	6.0
Period of study entry		
July 1994-June 1995	66	33.2
July 1995-June 1996	63	31.7
July 1996-July 1997	70	35.2
DSM-IV depression diagnosis		
No depression	164	82.4
Minor depression	17	8.5
Major depression	18	9.0
Median regimen toxicity score	2	
Range	0-8	
Graft-versus-host disease, grades 2-4	6	3.0
Documented infection	66	33.2

NOTE. Percentages may not sum up to 100% because of rounding.
Abbreviations: SCT, stem-cell transplantation; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition.
*Chronic lymphocytic leukemia (n = 7), myelodysplastic syndrome (n = 4), histiocytosis (n = 1), myeloproliferative syndrome (n = 1), and granulocytic sarcoma (n = 1).
†One syngeneic SCT was placed with the autologous SCT group.
‡Two patients with a combination of peripheral blood and bone marrow were included in this group.

for major and minor depression, respectively. Of the 164 patients with no diagnosis of depression, eight patients met symptom criteria for major depression and eight met symptom criteria for minor depression in at least one weekly interview, but they did not meet the corresponding temporal criterion of 2 consecutive weeks with major or minor depressive symptoms.

Thirteen patients were treated with antidepressants; seven were receiving treatment at the time of hospital admission, and six initiated their treatment during in-hospital follow-up. Of these seven patients receiving treatment at hospital admission, three were diagnosed with major depression (whether currently meeting criteria or in partial remission), and four were diagnosed with no current depression (maintenance antidepressant treatment was indicated for a past major depressive episode in two patients and a past minor depressive episode in two patients). Of the six patients who initiated treatment during in-hospital follow-up, three had major depression, and three were included in the no depression group, although they met DSM-IV criteria for adjustment disorder with mixed anxiety and depressed mood. Figure 1 displays unadjusted Kaplan-Meier survival curves showing the probability of 5-year survival after SCT according to DSM-IV depression status. Comparison of survival curves showed a pronounced mortality for major depression mainly within 3 years of SCT. The percentages of patients surviving at 1, 3, and 5 years were 50.0%, 33.3%, and 33.3%, respectively, for major depression; 94.1%, 75.3%, and 56.5%, respectively, for minor depression; and 77.4%, 60.4%, and 53.0%, respectively, for no depression.

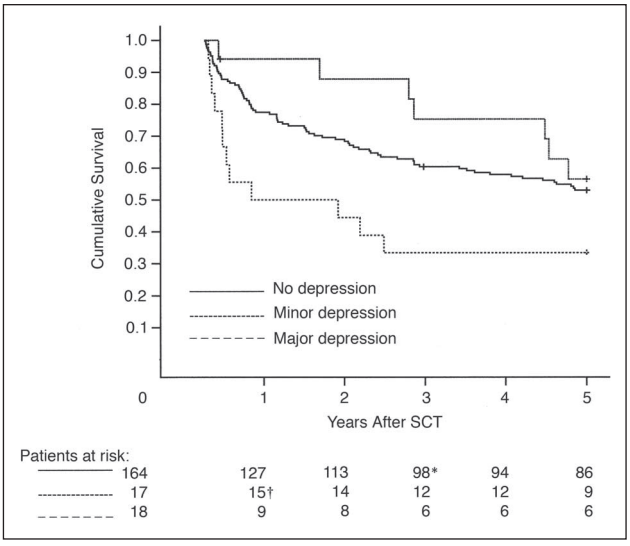

Fig 1. Unadjusted Kaplan-Meier survival curves showing the probability of 5-year survival after stem-cell transplantation (SCT) by Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, depression status. (*) One patient censored because of loss to further follow-up. (†) One patient censored because of a suicide death.

Table 2 lists all tested univariate predictors of 1-, 3-, and 5-year survival on univariate Cox regression analysis. All risk factors (except for the depression variable) with $P < .20$ in univariate analysis were included in a single multivariate model (data not shown). The factors found to be significant in this single multivariate model plus a term for the depression variable were all included in a final model. Table 3 lists the final multivariate Cox's regression models for 1-, 3-, and 5-year mortality. After adjusting for multiple confounding factors, major depression during hospitalization for SCT was associated with a greater risk of dying than no depression at 1 and at 3 years but not at 5 years. Interactions terms of the DSM-IV depression diagnoses variable and age, sex, disease risk, Karnofsky score, or regimen toxicity did not reach statistical significance in any mortality outcome.

In the 1- and 3-year multivariate mortality models, there was a trend for patients with minor depression to survive longer than patients with no depression (Table 3). To further explore the relationship between minor depression and mortality, we repeated the statistical analysis by using two different methods (data not shown), one of which was more flexible and other of which was more restrictive, to define the minor depression category. In the more flexible method, we included in the minor depression category the eight patients with no depression who met symptom criteria for minor depression of only 1 week in duration. In the more restrictive method, we excluded from analysis the six patients with minor depression who met symptom criteria for major depression of only 1 week in duration. By using these two different methods to define the minor depression category, we did not obtain a significant effect for minor depression in any of the 1-, 3-, or 5-year mortality models (all $P > .32$).

Comparing modified and unmodified DSM-IV approaches to diagnose depression, we found that two patients who met modified DSM-IV criteria for major depression were diagnosed with minor depression when unmodified DSM-IV criteria were applied and that two patients who met modified DSM-IV criteria for minor depression were diagnosed as nondepressive using unmodified DSM-IV criteria. Additional statistical analyses were performed in which depression was diagnosed by unmodified DSM-IV criteria. However, we have not reported these data because they are similar to the original analyses (Table 3).

We noted similar results when the survival analysis was confined to the 213 patients who survived longer than 30 days after SCT (data not shown). In model 1, the strength of the association between major depression and mortality was attenuated ($P = .043$ for 1-year mortality and $P = .09$ for 3-year mortality). In model 2, we did not find any significant interaction predicting 1- and 3-year mortality; the results were identical to those in model 1.

Table 2. Univariate Predictors of 1-Year, 3-Year, and 5-Year Mortality

Variable	1-Year Mortality		3-Year Mortality		5-Year Mortality	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age	1.01	0.99 to 1.04	1.02	1.00 to 1.04*	1.02	1.00 to 1.04*
Female	1.30	0.73 to 2.30	1.37	0.89 to 2.12†	1.35	0.91 to 2.03†
Married or living with partner	0.96	0.53 to 1.74	0.77	0.48 to 1.23	0.81	0.53 to 1.24
Education > 8 years	0.71	0.39 to 1.30	0.80	0.50 to 1.28	0.86	0.55 to 1.33
Karnofsky score < 90	1.87	0.90 to 3.86†	2.22	1.30 to 3.79‡	2.39	1.46 to 3.92§
Hematologic cancer diagnosis						
Acute lymphoblastic leukemia	2.23	0.94 to 5.25†	2.58	1.28 to 5.18‡	2.66	1.38 to 5.12‡
Chronic myelogenous leukemia	1.48	0.62 to 3.53	1.67	0.82 to 3.43†	1.72	0.86 to 3.42†
Lymphomas	0.72	0.24 to 2.13	0.90	0.42 to 1.92	0.80	0.40 to 1.63
Multiple myeloma	1.91	0.62 to 5.89	1.67	0.72 to 3.86	2.33	1.14 to 4.75*
Other diagnoses	0.86	0.24 to 3.13	1.20	0.46 to 3.10	1.30	0.54 to 3.15
Intermediate/high-risk status	1.61	0.87 to 2.95†	1.45	0.91 to 2.33†	1.57	1.01 to 2.43*
Peripheral-blood stem cells	0.63	0.35 to 1.15†	0.71	0.44 to 1.14†	0.73	0.47 to 1.14†
Chemoradiotherapy	2.35	0.87 to 6.40†	1.78	0.96 to 3.29†	1.66	0.97 to 2.82†
Smoking history	0.84	0.47 to 1.49	0.76	0.49 to 1.18	0.83	0.55 to 1.24
Dangerous alcohol intake	0.75	0.18 to 3.08	0.58	0.18 to 1.85	0.64	0.24 to 1.75
Period of study entry						
July 1995-June 1996	1.04	0.51 to 2.13	0.98	0.57 to 1.67	0.89	0.54 to 1.45
July 1996-July 1997	0.97	0.48 to 1.95	0.86	0.51 to 1.47	0.89	0.55 to 1.43
DSM-IV depression diagnosis						
Minor depression	0.21	0.03 to 1.56†	0.48	0.18 to 1.33†	0.74	0.34 to 1.61
Major depression	3.24	1.54 to 6.81‡	2.63	1.40 to 4.94‡	2.14	1.15 to 3.97*
Regimen toxicity	2.35	1.29 to 4.27‡	2.04	1.26 to 3.30‡	2.13	1.36 to 3.32§
GVHD, grades 2-4	1.69	0.51 to 5.56	1.94	0.69 to 5.46	1.88	0.67 to 5.29
Documented infection	0.92	0.48 to 1.74	0.86	0.53 to 1.41	0.79	0.50 to 1.25

NOTE. Because their median survival times were very similar, Hodgkin's disease and Non-Hodgkin's lymphoma were combined in the same lymphoma group, as were intermediate- and high-risk status. The comparison categories for variables with more than two categories were acute myelogeous leukemia, July 1994 to June 1995, and no depression. Coefficients for age are interpreted as increased risk per unit of time, and coefficients for regimen-related toxicity are interpreted as increased risk per 1-point score. All univariate models were stratified according to type of stem-cell transplantation.

Abbreviations: DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition; GVHD, graft-versus-host disease.

*$P < .05$.

†$P < .20$.

‡$P < .01$.

§$P < .001$.

DISCUSSION

To our knowledge, this is the largest oncologic study that uses standardized psychiatric diagnostic criteria to assess the impact of depression on mortality. After adjusting for multiple confounding factors, major depression during hospitalization for SCT was associated with a greater risk of dying than no depression at 1 and 3 years but not at 5 years.

The failure to detect a significant relationship between major depression and 5-year mortality might be related to the small number of major depressed patients, so that larger samples are needed to provide adequate statistical power. In a recent literature review of the impact of depression on cancer survival, it was reported that the average follow-up time in the positive studies was 5 years, whereas in the negative studies, the average follow-up time was 10 years.[9] One might conclude that studies with longer follow-up are more definitive, but this is not necessarily the case. Longer follow-up may be possible in less lethal forms of cancer. In our study, most patients died within the first 3 years after SCT.

Our results are consistent with those of other studies showing that depression significantly increases the risk of death in different noncancer samples.[1-3,5-8] Comparison with other oncologic studies of depression predicting mortality is difficult because of differences in research methodology.[4,9] Several recent methodologically rigorous studies have reported that depression as a single variable was predictive of shorter cancer survival.[10-13] However, none of these studies used standardized psychiatric criteria to diagnose depression.

We found a trend for patients with minor depression to survive longer than patients with no depression. However, when using a more flexible or a more restrictive method to define the minor depression category, we did not obtain significance or a trend towards significance in the association between minor depression and mortality. Most medical studies of the effect of baseline minor or subthreshold

Table 3. Multivariate Analysis of 1-Year, 3-Year, and 5-Year Mortality (final models)

Variable	1-Year Mortality			3-Year Mortality			5-Year Mortality		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age	1.00	0.97 to 1.03	.97	1.04	1.01 to 1.06	.002	1.04	1.02 to 1.06	< .001
Karnofsky score < 90				1.67	0.90 to 3.08	.102	1.79	1.02 to 3.13	.043
Hematologic cancer diagnosis						< .001			.001
Acute lymphoblastic leukemia				3.38	1.54 to 7.46	.002	3.27	1.54 to 6.95	.002
Chronic myelogenous leukemia				2.21	1.05 to 4.65	.036	2.07	0.99 to 4.33	.053
Lymphomas				0.56	0.25 to 1.28	.169	0.59	0.27 to 1.29	.187
Multiple myeloma				0.49	0.19 to 1.28	.146	0.79	0.34 to 1.84	.589
Other diagnoses				0.54	0.20 to 1.47	.227	0.61	0.24 to 1.55	.297
Intermediate/high-risk status							1.91	1.11 to 3.28	.019
Peripheral-blood stem cells							0.56	0.32 to 0.98	.042
DSM-IV depression diagnosis*			.009			.029			.267
Minor depression	0.17	0.20 to 1.25	.081	0.43	0.15 to 1.21	.111	0.65	0.29 to 1.43	.283
Major depression	2.59	1.21 to 5.53	.014	2.04	1.03 to 4.02	.041	1.48	0.76 to 2.87	.249
Regimen toxicity	1.47	1.21 to 1.79	< .001	1.25	1.05 to 1.49	.011	1.23	1.05 to 1.44	.009

NOTE. All risk factors (except for depression) with $P < .20$ in univariate analysis were included in a single multivariate model. The factors found to be significant in this single multivariate model plus a term for the depression variable were all included in final models. All models were stratified according to type of SCT. The proportional hazards assumption was met for all variables. See also footnotes of Table 2.

Abbreviations: DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition; SCT, stem-cell transplantation.

*By applying unmodified DSM-IV criteria, *P* values for major depression in 1-, 3-, and 5-year mortality were .022, .088, and .425, respectively, whereas *P* values for minor depression were .201, .165, and .425, respectively.

depression on mortality find no risk associated[1,10] or an increased risk of mortality.[2,3,7] After reviewing the literature, we found only one study that reported a significant association between subthreshold depression in women and decreased mortality.[26] However, in that study, a more severe level of depression was not associated with mortality. Furthermore, at a theoretical level, the difference between minor and major depression is not so great as to suggest that the mortality risk associated with these two diagnoses should diverge so widely. In our study, six of the 17 patients diagnosed with minor depression had symptom criteria for major depression of 1 week in duration. Therefore, we consider that the trend towards significance of the association between minor depression and decreased mortality risk is likely to be a spurious finding.

Some studies using patient-rated scale scores to define different levels of depression suggest that the severity of depression shows a gradient of risk for subsequent mortality.[2,3,7] In these studies, patients with minor or subthreshold depression displayed an intermediate pattern of survival that was between patients with no depression and patients with a more severe level of depression. It is likely that methodologic differences between studies contribute to the divergences in the findings regarding the association between minor or subthreshold depression and mortality. Given the limitation of patient-rated scales for evaluating only depressive symptoms present during the week preceding the interview, it is impossible to know whether patients diagnosed as having subthreshold depression in a particular study would correspond to patients with DSM-IV major depression in partial remission. Furthermore, there is evidence that long-term depression states are more likely to lead to adverse health outcomes than short-term ones.[1,2,5,9,13] In our study, we found that major depression episodes represented longer term depression states than minor depression episodes (median duration time, 45.5 *v* 6.0 weeks, respectively). It may be that the association between minor or subthreshold depression and increased mortality risk is, in part, mediated by a chronic course of these depressive symptoms.

Compared with our primary analysis of patients surviving longer than 90 days after SCT, the strength of the association between major depression and mortality was attenuated when the analysis was confined to patients surviving more than 30 days. In the SCT setting, where the highly intensive conditioning treatment is associated with an acute mortality risk, the role of depression may be more difficult to detect in the first few months after SCT because of the strong cancer- or treatment-related biologic processes during this stage.

The mechanisms that could mediate or explain the association between depression and mortality are not well understood.[9] First, depression may have direct pathophysiologic effects via neuroendocrine and immunologic functions that influence morbidity and mortality.[9,20,27-30] Second, depression may impact survival through behavioral mechanisms such as poorer adherence to medical treatment or health recommendations,[4,9,31,32] increased smoking and alcohol consumption,[4] and suicide.[4,17] Finally, disease progression or treatment side effects may cause or mimic depression.[9,19,20,23] However, our depression measures did not include somatic symptoms that could be attributed to the neoplastic process or cytotoxic treatment, and survival analyses controlled for

multiple confounding factors. Therefore, our results suggest that depression is not simply an artifact of declining health.

This study has several limitations. First, we did not measure inter-rater reliability, although we sought to maximize the reliability of our depression diagnoses by using standardized diagnostic criteria, serial observations, multiple sources of information, and discussion in regular meetings between investigators. Second, we did not measure several factors that could be predictors (eg, social support) or mediators (eg, treatment adherence) between depression and mortality. Third, the possible effects of psychiatric treatment on survival cannot be evaluated under the available study design. In such an observational sample, comparisons of outcomes based on treatment received are subject to substantial bias. Fourth, although our results provide additional support for the prognostic importance of depression, they do not establish that depression causes fatal cancer- or treatment-related events. For instance, we do not know whether patients who were depressed in the hospital were still depressed at the time of their deaths up to 5 years later. To establish a causal relationship, we need to perform longitudinal research combining repeated measurement of depression and its presumed pathophysiologic mechanisms, followed by adequately powered, randomized trials targeting the mechanisms implicated. Finally, the association between depression and disease outcome is based on a relatively small sample of major depressed patients. However, this association is strengthened by high recruitment and follow-up rates and a comprehensive set of clinical confounding variables considered for risk adjustment. Moreover, the use of a rigorous psychiatric diagnostic method coupled with serial evaluations increased the accuracy of depression diagnosis.

Coupled with the widespread tendency to excuse depression as an understandable and inevitable reaction to cancer and the consequent risk for depression underdiagnosis and undertreatment,[33,34] our findings highlight the critical importance of early recognition and treatment of major depression. Because of the substantial prevalence and chronicity of major depression at hospital admission, it would be better to conduct a first assessment after the patient agrees to undergo SCT. In cancer populations, the effect of psychopharmacologic and psychological interventions on treating depression has been reviewed and shown to be beneficial.[9,19,20,35,36] Although a considerable body of research exists, the question of whether psychosocial intervention has a beneficial effect on cancer survival remains unresolved.[9,37-39] However, most of these intervention studies were designed to reduce distress in general and enhance coping rather than treat depressive disorders per se. Although it remains to be determined whether early recognition and effective treatment of major depression result in longer survival, they do have the potential to improve health care outcomes, reduce patient suffering, and enhance quality of life.[9,19,20,35-37]

Acknowledgment

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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5. RESULTATS

De forma preliminar informar que es produeixen unes variacions en el nombre total de pacients analitzats i de les avaluacions psicomètriques o psiquiàtriques realitzades en funció dels objectius específics de cadascun dels articles publicats.

La mostra total d'estudi és de 220 pacients, no obstant en l'anàlisi de l'impacte de la patologia psiquiàtrica en el temps d'estada hospitalària la mostra d'estudi fou de 208 pacients doncs s'exclogueren 12 pacients que moriren durant el període d'hospitalització. Així mateix, en l'anàlisi de l'impacte de la depressió major en la mortalitat posttrasplantament la mostra d'estudi fou de 199 pacients doncs s'exclogueren 21 pacients que moriren en el període de tres mesos posteriors a la data de trasplantament.

Des de la primera valoració en el moment de l'ingrés fins el moment de l'alta o mort, es realitzaren un nombre total de 1062 valoracions psiquiàtriques i 1064 valoracions mitjançant el grup de qüestionaris autoadministrats. Malgrat això, en l'anàlisi de l'evolució de les variables físiques i psicològiques durant la fase d'hospitalització així com en l'anàlisi dels factors clínics associats amb la fatiga, amb una mostra de pacients de 220, es tingué només en compte les avaluacions realitzades en el moment de l'ingrés (T1) i les tres avaluacions setmanals posteriors (T2, T3, i T4), representant un total de 852 valoracions. Fer també esment, que en l'anàlisi de l'impacte de la depressió major en la mortalitat posttrasplantament, amb una mostra de pacients de 199, s'utilitzà també les quatre primeres avaluacions (T1-T4) representant un total de 781 valoracions psiquiàtriques. En aquests tres estudis, la raó per utilitzar únicament les quatre primeres avaluacions fou per evitar la gran pèrdua de pacients ("dropouts") que es produeix de forma posterior a T4 a conseqüència de les altes hospitalàries.

Havent realitzat aquestes aclaracions, a continuació presentem els resultats que apareixen en l'apartat *"Abstract"* de cadascuna de les sis publicacions de l'actual tesi:

5.1 Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation.

En l'anàlisi de les propietats psicomètriques de les quatre escales de qualitat de vida dissenyades pel nostre grup de recerca, es demostrà mitjançant l'anàlisi de consistència interna i de l'estabilitat test-retest que la fiabilitat fou adequada. En l'anàlisi sobre la validesa de convergència, de divergència, de criteri i predictiva així com en l'anàlisi de la sensibilitat al canvi es varen demostrar en tots els casos associacions significatives amb els constructes de referència.

5.2 Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation.

En la mostra total de la població, el nivell HADS d'ansietat fou màxim en el moment de l'admissió hospitalària i decreixent de forma posterior; un marcat empitjorament de les variables d'estat físic es va correspondre amb un increment agut en els nivells HADS de depressió del moment de l'admissió hospitalària fins la primera setmana posttrasplantament, seguint-se posteriorment per una millora de l'estat físic i reducció paral·lela dels nivells HADS de depressió. El grup de pacients trasplantats autòlegs, en comparació amb el al·logènics, van presentar una evolució més favorable en relació a les variables d'estat físic, demostrant-se en l'anàlisi de variància de mesures repetides mitjançant l'efecte de grup significatiu en l'escala de simptomatologia sistèmica i per la interacció significativa entre els factors de grup i temps en les escales d'estat físic global i de nivell d'energia; en relació als nivells i evolució dels símptomes HADS de depressió i d'ansietat no s'apreciaren diferències significatives entre els dos grups de pacients trasplantats.

5.3 Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation.

En l'anàlisi multivariant transversal, realitzada mitjançant regressió lineal en els quatre primers punts d'avaluació hospitalària, la variable símptomes depressius avaluada segons l'escala HADS fou el factor de risc que s'associà amb el nivell més alt de significació i consistència amb la variable fatiga; altres factors de risc associats de forma significativa amb fatiga en qualsevol dels quatre punts d'avaluació foren edat avançada, nivell d'estudis alt, fumador, baix estat funcional, pèrdua de gana, nàusees/vòmits, dolor, elevada toxicitat relacionada amb el règim de condicionament, baix nivell d'hemoglobina, requeriment de transfusions de concentrats

d'hematies i tercer any del període d'estudi. En l'anàlisi multivariant prospectiva, realitzada mitjançant regressió lineal, la valoració basal de símptomes depressius realitzada en el moment de l'ingrés hospitalari va mostrar una significació o una tendència a la significació en la seva capacitat per a predir les tres mesures subseqüents de fatiga durant el curs de l'hospitalització.

5.4 Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation.

La prevalença de trastorn psiquiàtric global segons criteris DSM-IV fou del 44.1%; el trastorn adaptatiu es diagnosticà en un 22.7% dels pacients, el trastorn de l'estat d'ànim en un 14.1%, el trastorn d'ansietat en un 8.2% i el delirium en un 7.3%. Mitjançant anàlisi de regressió lineal multivariant i després d'ajustar per un seguit de factors de risc de confusió, els factors associats de forma significativa amb un increment en l'estada hospitalària foren: diagnòstic de trastorn psiquiàtric (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) ($P = .022$); leucèmia mielogènica crònica ($P = .003$); valor de l'estat funcional de Karnofsky en el moment de l'admissió hospitalària < 90 ($P = .025$); i elevada toxicitat relacionada amb el règim de condicionament ($P < .001$). Per altra banda, els factors associats de forma significativa amb un decrement en l'estada hospitalària foren: leucèmia limfoblàstica aguda ($P = .009$), limfoma no-Hodgkin ($P = .04$), ús de cèl·lules progenitores de sang perifèrica ($P < .001$), segon any del període d'estudi ($P < .001$) i tercer any del període d'estudi ($P < .001$).

5.5 Stem cell transplantation: risk factors for psychiatric morbidity.

La prevalença de trastorn psiquiàtric (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) segons criteris DSM-IV en el moment de l'admissió hospitalària fou del 20.9% i la incidència de trastorn psiquiàtric durant el seguiment hospitalari posterior fou del 22.4%. En l'anàlisi multivariant de regressió logística, i després d'ajustar per múltiples variables de confusió, trobàrem que els factors associats amb un increment de risc de patir trastorn psiquiàtric foren: edat jove, dona, antecedents d'historial psiquiàtric, baix estat funcional, dolor, retirada del consum de tabac en el moment de l'admissió hospitalària i elevada toxicitat relacionada amb el règim de condicionament.

5.6 Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation.

Divuit (9.0%) pacients compliren criteris DSM-IV de depressió major i disset (8.5%) de depressió menor durant la fase d'hospitalització per a realitzar el trasplantament de progenitors hemopoètics. En models de regressió de Cox multivariants es va evidenciar que la depressió major fou predictiva d'un increment de la mortalitat a l'any (raó de taxes [RT], 2.59; interval de confiança del 95% [IC 95%], 1.21-5.53; P = .014) i al tercer any (RT, 2.04; IC 95%, 1.03-4.02; P = .041), sense cap influència en la mortalitat al cinquè any posttrasplantament (RT, 1.48; IC 95%, 0.76-2.87; P = .249). La depressió menor no va demostrar cap efecte en la mortalitat. Altres factors de risc que es manifestaren com a predictors significatius d'un increment en la mortalitat foren: elevada toxicitat pel règim de condicionament en els models predictius de mortalitat al primer, tercer i cinquè any posttrasplantament; edat avançada i leucèmia limfoblàstica aguda en els models predictius al tercer i cinquè any; leucèmia mielogènica crònica en el model predictiu al tercer any; baix estat funcional i risc de malaltia elevat/entremig en el model predictiu al cinquè any. L'ús de cèl·lules progenitores de sang perifèrica fou predictiva d'una reducció en la mortalitat al cinquè any posttrasplantament.

6. DISCUSSIÓ

De forma prèvia a la presentació dels aspectes de la discussió més rellevants de cadascuna de les publicacions, es descriuen algunes de les limitacions i qualitats del global de la investigació.

Com a limitacions esmentar: 1) La no mesura de la funció cognitiva dels pacients. Malgrat que la disfunció cognitiva pot afectar els resultats dels qüestionaris autoadministrats, en el nostre estudi es van excloure aquells pacients que en el moment de l'entrevista psiquiàtrica presentaven una afectació de les seves funcions psíquiques. 2) La no valoració multidimensional de la fatiga. Malgrat aquest fet, les avantatges d'utilitzar una escala d'un ítem valorant fatiga inclouen una mínima sobrecàrrega pel pacient, la simplicitat i la facilitat en l'ús clínic. 3) El fet que els psiquiatres de l'equip de recerca també foren els mateixos que proporcionaren l'atenció psiquiàtrica podria haver afectat les respostes dels pacients en els qüestionaris. Malgrat això, en la segona publicació de la tesi s'analitzà l'efecte d'excloure aquells pacients que reberen tractament psicofarmacològic i es mostrà que els resultats estadístics i patrons evolutius dels símptomes depressius i d'ansietat foren molt similars en la mostra de pacients no tractats comparat amb la mostra total. 4) L'estudi només d'un nombre limitat de trastorns psiquiàtrics (trastorn adaptatius, de l'estat d'ànim i d'ansietat), a fi i efecte d'evitar una sobrecàrrega al pacient durant la fase de trasplantament. Aquests trastorns però, suposen la gran part de la patologia psiquiàtrica que presenten els pacients amb càncer (2-7,82). 5) Malgrat no es va avaluar la fiabilitat entre els entrevistadors, varem tractar d'incrementar al màxim la fiabilitat dels nostres diagnòstics psiquiàtrics mitjançant la utilització de criteris diagnòstics estandarditzats, valoracions setmanals, diverses fonts d'informació i la discussió entre els entrevistadors per arribar a un diagnòstic consensuat. 6) L'ús d'una variable psiquiàtrica global (tercera i quarta publicacions) que inclou al mateix temps el grup de trastorns adaptatius, trastorns de l'estat d'ànim i trastorns d'ansietat ve justificada per la freqüent coexistència de símptomes depressius i d'ansietat (3,4,8,82), per la tendència durant la fase d'hospitalització del trasplantament a l'evolució d'un diagnòstic inicial de trastorn adaptatiu cap a un diagnòstic final de trastorn depressiu o d'ansietat (18% de la nostra mostra) i per a incrementar la mostra de pacients psiquiàtrics a fi i efecte de reduir la possibilitat que es produís un error estadístic tipus II (fals negatiu o incapacitat de mostrar una diferència significativa quan en realitat existeix). 7) La no valoració de suport social, possible predictor de trastorn psiquiàtric o de mortalitat, o del compliment terapèutic, variable que podria ser mediadora de la relació entre depressió i mortalitat. No es va poder analitzar l'efecte del suport social donat que l'escala validada

d'aïllament social (Nottingham Health Profile [77]) utilitzada en el nostre estudi va obtindre una baixa puntuació en l'anàlisi de consistència interna (alfa de Cronbach). 8) El disseny del nostre estudi no permet el poder analitzar els possibles efectes del tractament psiquiàtric en la supervivència. En una mostra observacional com la nostra, la comparació dels resultats en base als tractaments rebuts està subjecte a un important biaix. 9) Malgrat que els nostres resultats proporcionen un suport addicional a la importància de la depressió major com a factor pronòstic de la mortalitat, en realitat no estableixen que la depressió major sigui causa directa de la mortalitat. Per establir una relació causal, precisem d'un estudi longitudinal on es realitzin valoracions repetides de la depressió major i alhora del mecanismes fisiopatològics subjacents, posteriorment seguit dels assajos randomitzats pertinents on específicament s'estudiïn els mecanismes implicats. 10) L'associació entre depressió major i mortalitat es basa en una mostra relativament reduïda de pacients. 11) Com en qualsevol investigació realitzada en una única institució, les conclusions obtingudes són específiques del nostre centre i reflecteixen les característiques dels nostres pacients i els patrons de pràctica clínica.

Malgrat les limitacions descrites, els resultats exposats en la present tesi es veuen en part reforçats per les qualitats positives a nivell metodològic: disseny prospectiu, mostra no biaixada, alt nivell de participació, mostra total de pacients elevada (n = 220), ús de qüestionaris breus i prèviament validats, utilització de tècniques estadístiques multivariants que controlen l'efecte d'un ampli nombre de possibles variables de confusió. En afegiment, l'ús d'un mètode diagnòstic aplicat amb rigor (entrevista psiquiàtrica estructurada seguint criteris diagnòstics DSM-IV) associat a les avaluacions setmanals realitzades durant el procés d'hospitalització (total de 1062 valoracions psiquiàtriques) incrementen la precisió en el diagnòstic psiquiàtric.

A continuació presentem alguns dels aspectes més rellevants de l'apartat "Discussió" de cadascuna de les publicacions de l'actual tesi:

6.1 Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation

Les quatre escales de qualitat de vida dissenyades pel nostre grup de recerca són les primeres en ser validades pel seu ús en població adulta durant el període d'hospitalització per a realitzar el trasplantament de progenitors hemopoètics. Durant aquest període, associat a un gran nombre d'estressors físics i psíquics, una

consideració molt important a tenir compte és el risc de sobrecàrrega en el pacient com a conseqüència d'haver de respondre a qüestionaris de qualitat de vida sovint molt extensos. La inversió en temps que representa pel pacient el completar les quatre escales de l'estudi fou d'un minut aproximadament. Així doncs, la simplicitat i facilitat d'administració d'aquests instruments els fa particularment atractius pel seu ús durant la fase d'hospitalització. La validació d'aquestes escales suposa un pas previ a la investigació de factors de risc i curs evolutiu d'alguns dels paràmetres valorats per aquestes mateixes escales, presentant-se aquestes dades en les dues següents publicacions del nostre grup de recerca.

6.2 Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation

La investigació actual representa l'estudi més extens publicat fins el moment, en el que s'analitza diversos aspectes de funcionament físic i psíquic durant la fase d'hospitalització per a realitzar el trasplantament de progenitors hemopoètics.

En base al curs evolutiu que presenten els símptomes depressius i d'ansietat en la nostra mostra de població, es suggereix que un abordatge ideal en la fase prèvia a l'ingrés hospitalari podria englobar tant una valoració psicosocial exhaustiva com la implementació d'intervencions dirigides a reduir l'alt nivell d'ansietat pretrasplantament. Donat que l'ansietat està sovint associada a una informació incorrecta o insuficient, els aspectes educatius i d'informació relacionats amb el procés de trasplantament adquireixen una especial rellevància (5).

La monitorització setmanal de símptomes depressius i d'ansietat durant la fase d'hospitalització ens pot ajudar a identificar aquells pacients que es poden beneficiar d'una valoració i/o atenció psiquiàtrica. Donada la ja considerable càrrega associada amb el procés de trasplantament, el reconeixement precoç i tractament dels problemes emocionals es constitueixen com a objectius importants en la pràctica clínica. El desenvolupament i avaluació d'intervencions específiques de tractament es beneficien tant del coneixement del curs evolutiu com dels factors de risc de les variables psicològiques.

6.3 Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation

En base als resultats del present estudi, es dóna suport a l'etiologia multidimensional de la fatiga. Malgrat que alguns dels factors que es troben associats amb la fatiga no siguin modificables, altres factors són susceptibles d'ésser tractats i poden resultar en un decrement dels nivells de fatiga. Des d'un punt de vista clínic, fem especial esment a la importància de realitzar un cribatge acurat de la depressió en aquells pacients amb càncer que presentin queixes de fatiga. Qüestionaris autoadministrats, breus i simples com el HADS poden ser d'utilitat per a la detecció de la depressió en la pràctica clínica oncològica (79,80,84). Altres estratègies per a reduir els nivells de fatiga estarien en relació a un tractament apropiat del dolor, de les nàusees/vòmits, de l'anèmia i del tabaquisme.

6.4 Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation

La investigació actual representa l'estudi hospitalari més extens publicat en la literatura oncològica general on mitjançant l'ús de criteris diagnòstics psiquiàtrics estandarditzats i valoracions longitudinals s'estima la prevalença de trastorn psiquiàtric.

S'indica segons criteris DSM-IV una alta prevalença de trastorn psiquiàtric, en especial ja des del moment de l'admissió hospitalària, i l'associació de la patologia psiquiàtrica amb un increment de l'estada hospitalària. En relació a les troballes del present estudi, es suggereix el realitzar una valoració psiquiàtrica exhaustiva de forma prèvia a l'admissió hospitalària. L'alta prevalença de trastorn psiquiàtric incrementa la utilitat pràctica d'un programa de cribatge doncs es produeix un augment en el valor predictiu positiu de la prova (és a dir, augmenta la probabilitat de que el pacient tingui realment un trastorn psiquiàtric si es detecta com a cas). Una avantatge de l'homogeneïtat dels trastorns psiquiàtrics estudiats es que pot permetre l'aplicació d'estudis d'intervenció específics i fàcilment replicables. En pacients amb càncer, s'ha revisat i alhora demostrat un efecte beneficiós de les intervencions psicofarmacològiques i psicològiques emprades (2-5,7,64,85,86).

6.5 Stem cell transplantation: risk factors for psychiatric morbidity

La possibilitat d'introducció d'estratègies exitoses de prevenció de trastorn psiquiàtric (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) es veu en part limitada pel fet que la gran part dels factors de risc de trastorn psiquiàtric són poc modificables (edat jove, dona, antecedents d'historial psiquiàtric, baix estat funcional, elevada toxicitat). Malgrat aquest fet, els resultats de l'estudi poden ser d'utilitat pel clínic de cares a facilitar una millora en el reconeixement d'aquells pacients amb risc de desenvolupar un trastorn psiquiàtric durant la fase de trasplantament.

Dos factors de risc de trastorn psiquiàtric que són susceptibles d'ésser modificats són el dolor i el tabaquisme. En base als resultats d'aquest article es fa evident la importància de l'actuació del clínic alhora de reduir la patologia psiquiàtrica en base a l'intervenció del dolor. Una altra de les troballes significatives del present estudi fa referència a que la retirada del consum de tabac coincidint amb l'ingrés hospitalari prediu de forma significativa l'aparició de trastorn psiquiàtric durant el període de seguiment hospitalari. La presència de casos d'aparició de depressions severes coincidint amb la retirada del tabac i que poden ser revertits pel reinici del consum, la necessitat de tractament antidepressiu de manteniment en determinats fumadors abstinents i l'aparició desproporcionada de símptomes depressius i d'ansietat en determinats pacients durant la retirada del tabac (64,87), són dades que reforcen l'observació que els pacients fumadors amb càncer presenten un risc incrementat de presentar patologia psiquiàtrica de forma posterior a la retirada del consum tabac. Així doncs, la intervenció de serveis especialitzats en el tractament del tabaquisme poden ser d'utilitat en la promoció de la salut tant física com psíquica.

6.6 Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation

La investigació actual representa l'estudi més extens publicat en la literatura oncològica general on mitjançant l'ús de criteris psiquiàtrics estandarditzats s'avalua l'impacte de la depressió en la mortalitat.

En el moment actual no es coneixen amb claredat els mecanismes que podrien explicar l'associació entre la depressió en pacients amb càncer i la mortalitat (7). La depressió podria tenir uns efectes fisiopatològics directes via funcions immunològiques i neuroendocrines que podrien influenciar en la morbiditat i mortalitat (7,64,88-91). Per altra banda, la depressió podria impactar en la supervivència: a) a través de mecanismes conductuals com podrien ser una pobra

adherència al tractament mèdic pautat o a les recomanacions de salut (7,19,20,92); b) a través de conductes freqüentment associades amb la depressió com són el consum de tabac i d'alcohol (92); c) com a conseqüència del suïcidi (3,92). Finalment també considerar la possibilitat que la progressió de la malaltia o els efectes secundaris del tractament poden causar o imitar els símptomes de la depressió (3,7,64,83). Malgrat tot, el mètode modificat de diagnòstic de depressió major que hem utilitzat en el present estudi no inclou símptomes somàtics que puguin ser atribuïts al procés neoplàsic o al tractament citotòxic, i en afegiment, en l'anàlisi multivariant de supervivència s'ha controlat l'efecte de múltiples factors mèdics de confusió. Així doncs, els nostres resultats suggereixen que la depressió major no és simplement un artefacte d'un mal estat de salut.

En base als resultats del present estudi es fa esment a la importància de realitzar una detecció precoç i tractament adequat de la depressió major, a fi i efecte de disminuir l'impacte negatiu que pot suposar pel pacient. Malgrat que existeixi una literatura considerable, queda avui en dia encara per resoldre si existeix un efecte beneficiós de les intervencions psicosocials en la supervivència relacionada amb el càncer. La gran majoria dels estudis d'intervenció existents han estat dissenyats per a aconseguir una reducció d'estrès en general i per a afavorir l'afrontament a la malaltia, més que tractar de forma específica els trastorns depressius. Malgrat quedi per determinar si una detecció precoç i un adequat tractament de la depressió major en pacients amb càncer resulti en una supervivència incrementada, si que pot representar un avenç en la pràctica mèdica, una reducció en el patiment emocional i una millora en la qualitat de vida del pacient (3,7,64,93-95).

7. CONCLUSIONS

En aquest apartat es descriuen les conclusions referents a cadascuna de les sis publicacions que constitueixen la present tesi:

7.1 Psychometric study of quality of life instruments used during hospitalization for stem cell transplantation

Es demostra la validesa i fiabilitat de les quatre escales de qualitat de vida dissenyades pel nostre grup de recerca pel seu ús en la fase d'hospitalització per a realitzar el trasplantament de progenitors hemopoètics

7.2 Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation

Segons el qüestionari autoadministrat HADS, el nivell d'ansietat és màxim en el moment de l'ingrés hospitalari mentre el nivell de depressió ho és en la primera setmana posttrasplantament. Inicialment un empitjorament dels paràmetres físics es correspon amb un increment dels nivells de depressió, seguint-se posteriorment d'una millora de l'estat físic i reducció dels nivells de depressió. En comparació amb el grup de trasplantats al·logènics, els grup de trasplantats autòlegs presenta un curs evolutiu més favorable a nivell físic sense evidenciar-se diferències en relació als símptomes depressius i d'ansietat. En base a aquests resultats es pot orientar en l'adopció de determinades decisions de tractament, facilitar l'afrontament al procés de trasplantament i millorar en el disseny d'estratègies de prevenció i tractament.

7.3 Clinical factors associated with fatigue in haematologic cancer patients receiving stem-cell transplantation

Entre múltiples factors de risc significatius, la variable símptomes depressius avaluada segons el HADS és el factor que s'associa amb el més alt nivell de significació i consistència amb la variable fatiga durant la fase hospitalària del trasplantament. Les troballes d'aquest article poden ser d'utilitat per a esclarir els mecanismes subjacents a la fatiga i alhora servir de guia per a futures intervencions de tractament de la fatiga relacionada amb el càncer. Des d'un punt de vista més clínic, es subratlla la importància de realitzar un cribatge

acurat de la depressió en aquells pacients amb càncer que presentin queixes de fatiga.

7.4 Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation

Durant la fase d'hospitalització del trasplantament un 44.1% de la població d'estudi presenta un trastorn psiquiàtric segons criteris DSM-IV. El trastorn adaptatiu es diagnostica en un 22.7% dels pacients, el trastorn de l'estat d'ànim en un 14.1%, el trastorn d'ansietat en un 8.2% i el delirium en un 7.3%. Després d'ajustar per múltiples factors de risc de confusió, el diagnòstic de trastorn psiquiàtric (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) s'associa de forma significativa amb un increment de l'estada hospitalària. En relació a aquests resultats, es fa especial esment a la necessitat d'una detecció precoç i d'un tractament efectiu de la patologia psiquiàtrica.

7.5 Stem cell transplantation: risk factors for psychiatric morbidity

Després d'ajustar per múltiples variables de confusió, els factors associats amb un increment de risc de patir un trastorn psiquiàtric (trastorn adaptatiu, de l'estat d'ànim o d'ansietat) durant la fase hospitalària del trasplantament són: edat jove, dona, antecedents d'historial psiquiàtric, baix estat funcional, dolor, retirada del consum de tabac i elevada toxicitat del tractament citotòxic. Els resultats d'aquest estudi poden ser d'utilitat pel clínic a fi i efecte de facilitar una millora en el reconeixement d'aquells pacients amb risc de presentar un trastorn psiquiàtric durant la fase de trasplantament.

7.6 Role of depression as a predictor of mortality among cancer patients after stem-cell transplantation

Divuit (9.0%) pacients compleixen criteris DSM-IV de depressió major i disset (8.5%) de depressió menor durant la fase d'hospitalització pel trasplantament de progenitors hemopoètics. Després de controlar l'efecte de múltiples factors de confusió, la depressió major prediu de forma significativa un increment de la mortalitat a l'any i al tercer any, sense cap influència en la mortalitat al cinquè any posttrasplantament. La depressió menor no demostra cap efecte en la mortalitat. En base als resultats d'aquest estudi, es fa especialment esment a la importància de diagnosticar i tractar de forma adequada la depressió major.

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