

Il Trapianto e le Terapie Cellulari : presente e futuro

...oltre il pessimismo clinico

Traiettorie prognostiche, supporto vitale e il nuovo paradigma di appropriatezza in Terapia Intensiva



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Castelfranco Veneto, 19 Ottobre 2026



Conflict of Interest Disclosure



Quadro Sinottico degli Argomenti



01. Epidemiologia



02. Cause di Ricovero



03. Score Prognostici



04. Appropriatelyzza

.....l'entità del problema ?

HEMATOLOGY

2025, VOL. 30, NO. 1, 2569149

<https://doi.org/10.1080/16078454.2025.2569149>



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Sepsis and organ failure are the major risks for allogeneic transplant patients in the post- or late- engraftment phase admitted to the ICU

Michael Serries^{a,b*}, Lisa Faßbender^{a,b*}, Hannah Zenzen^{a,b}, Mario Heine^{a,b}, Tobias A. W. Holderried^{a,b}, Peter Brossart^{a,b} and Katjana Schwab^{a,b}

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become a widely used approach to hematological diseases. Despite improvements in survival rates [1–3] studies suggest that 10–55% of allo-HSCT recipients require intensive care management [4,5]. The mortality rates in the Intensive Care Unit (ICU) vary but remain high, reaching up to 65% [6]. However, recent data shows a similar long-term survival in patients who survive their ICU-stay compared to patients who have never been admitted to the ICU [2,7].

Percentuale di Ricovero in Terapia Intensiva

2,5%

Percentale su tutti i ricoveri in ICU

Frequenza significativamente superiore (>20%) rispetto al trapianto autologo.

Mediana Temporale

Ricovero a circa 85 giorni dall'infusione delle cellule staminali.

Finestra a Maggior Rischio

Oltre il 70% degli ingressi avviene entro il primo anno dal trapianto.

Sopravvivenza a Lungo Termine

Dubbia visto la variabilità della presentazione clinica .

Fasi temporali e Presentazioni cliniche

PERIODO PRECOCE (30-100 GIORNI)

Fase di Pre-Engraftment

Aplasia Midollare: Neutropenia profonda e mucosite severa.

Sepsi Batterica: Shock settico da germi Gram-negativi.

Tossicità : Danno endoteliale e sindrome da attecchimento (PERDS).



Complicanze Infettive

PERIODO TARDIVO (> 100 GIORNI)

Fase di Post-Engraftment

GvHD Grave: Attacco epiteliale cutaneo e gastrointestinale e polmonare (Bronchiolite Obliterante e Polmonite Organizzativa)

Infezioni Opportunistiche: Riattivazioni da CMV, funghi e PCP.

Insufficienza Multiorgano: Scompenso tardivo a prognosi complessa.



Complicanze Immunologiche



Polmonite Idiopatica (IPS) , Emorragia Alveolare Diffusa (FAH), Bronchiolite Obliterante (BOS), Polmonite Organizzativa (OP)

Motivi di Ammissione in Terapia Intensiva

69%

Insufficienza Respiratoria

Principale trigger per l'accesso intensivo.

62%

Danno Renale Acuto

Tossicità da farmaci e disidratazione severa.

42%

Shock Settico

Ipotensione refrattaria e acidosi lattica.

14%

Tossicità Neurologica

Encefalopatia e complicanze da CNI.

Fattori di Rischio ed Indicatori Prognostici

Outcomes in Critically Ill Allogeneic Hematopoietic Stem-Cell Transplantation Recipients

Antoine Lafarge¹, Thibault Dupont¹, Emmanuel Canet³, Anne-Sophie Moreau⁵, Muriel Picard⁶, Djamel Mokart⁸, Laura Platon⁹, Julien M... Anne Renault¹⁵, Régis... Naïke Bigé¹⁶, and Elie...

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Methods: We investigated outcomes and determinants of mortality in a large multicenter retrospective cohort of Allo-HSCT patients admitted between January 1, 2015, and December 31, 2020, to 14 French ICUs. The primary endpoint was 90-day mortality.

Measurements and Main Results: In total, 1,164 patients were admitted throughout the study period. At the time of ICU admission, 765 (66%) patients presented with multiple organ dysfunction, including acute respiratory failure in 40% (*n* = 461). The median sepsis-related organ failure assessment score was 6 (interquartile range, 4–8). Invasive mechanical ventilation, renal replacement therapy, and vasopressors were required in 438 (38%), 221 (19%), and 468 (41%) patients, respectively. ICU mortality was 26% (302 deaths). Ninety-day, 1-year, and 3-year

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I 5 Fattori di Rischio di aumentata mortalità a 90 giorni

OR 2.0 · $p < 0.001$

Età > 56 Anni

Raddoppio del rischio relativo di decesso a 90 giorni.

OR 1.68 · $p = 0.005$

Timing 30–90 gg

Fase critica di transizione immunologica post-trapianto.

OR 1.63 · $p < 0.001$

aGvHD Refrattaria

Mancata risposta al trattamento steroideo di prima linea.

OR 1.9 · $p < 0.001$

Necessità di Vasopressori

Segno di shock vasoplegico o cardiogeno refrattario.

OR 3.1 · $p < 0.001$

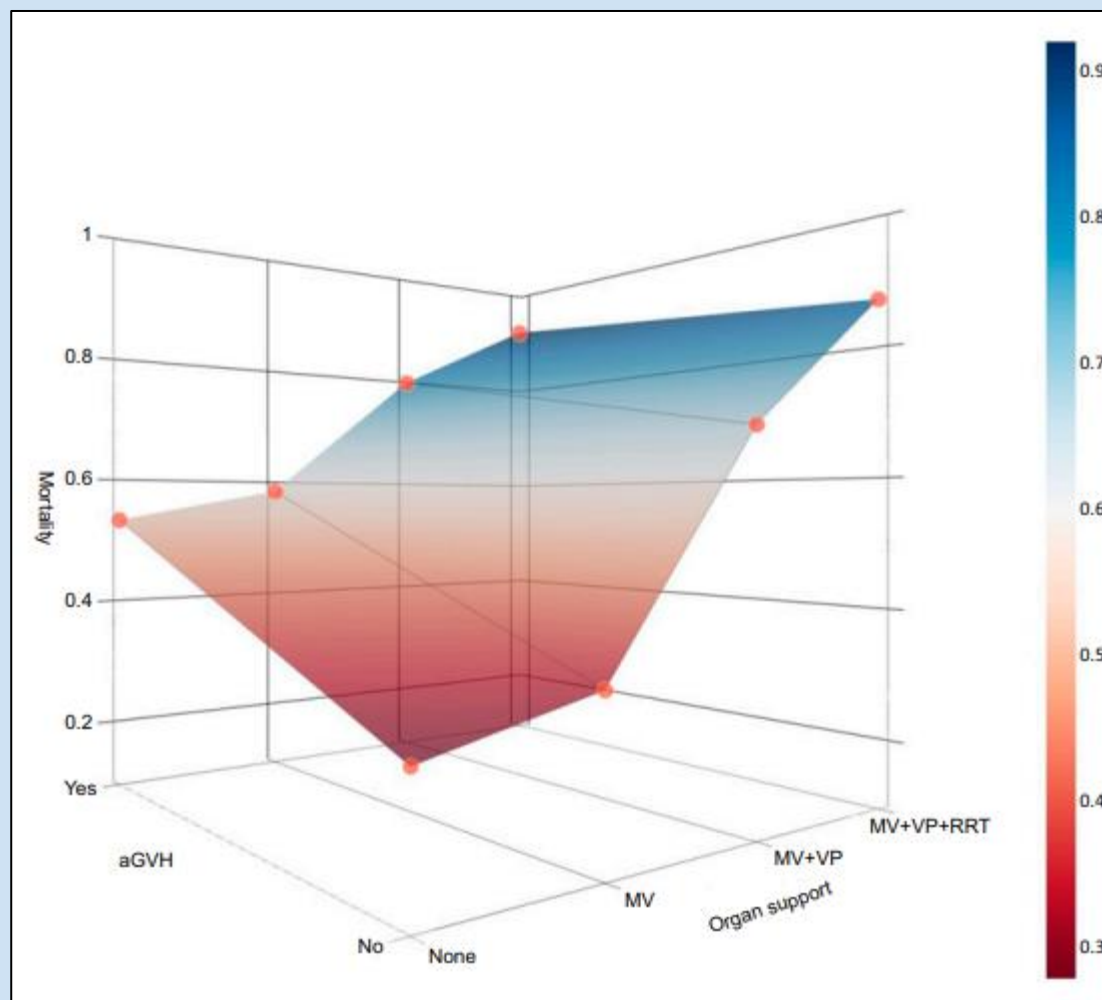
Necessità di supporto ventilatorio (IMV >>> NIMV)

Mortalità dal 39% (senza altri fattori) al 100% (4 fattori associati).

...tutti devono essere ricoverati in Terapia Intensiva ???

Parametro Clinico	Soglia Critica	Impatto sulla Mortalità	
SOFA Score	> 7 punti	Aumento significativo (p = 0.033)	
APACHE-II Score	> 14 punti	Correlazione infausta (p = 0.017)	

Mortalita' aGVH a 90 giorni



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Indicatori Prognostici di Esito Clinico e Fattori di Rischio

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Abstract

Rationale: Allogeneic hematopoietic stem-cell transplantation (Allo-HSCT) recipients are still believed to be poor candidates for ICU management.

Methods: We investigated outcomes and determinants of mortality in a large multicenter retrospective cohort of Allo-HSCT patients admitted between January 1, 2015, and December 31, 2020, to 14 French ICUs. The primary endpoint was 90-day mortality.

Measurements and Main Results: In total, 1,164 patients were admitted throughout the study period. At the time of ICU admission, 765 (66%) patients presented with multiple organ dysfunction, including acute respiratory failure in 40% ($n = 461$). The median sepsis-related organ failure assessment score was 6 (interquartile range, 4–8). Invasive mechanical ventilation, renal replacement therapy, and vasopressors were required in 438 (38%), 221 (19%), and 468 (41%) patients, respectively. ICU mortality was 26% (302 deaths). Ninety-day, 1-year, and 3-year

mortality rates were 48%, 63%, and 70%, respectively. By multivariable analysis, age > 56 years (odds ratio [OR], 2.0 [95% confidence interval (CI), 1.53–2.60]; $P < 0.001$), time from Allo-HSCT to ICU admission between 30 and 90 days (OR, 1.68 [95% CI, 1.17–2.40]; $P = 0.005$), corticosteroid-refractory acute graft-versus-host disease (OR, 1.63 [95% CI, 1.38–1.93]; $P < 0.001$), need for vasopressors (OR, 1.9 [95% CI, 1.42–2.55]; $P < 0.001$), and mechanical ventilation (OR, 3.1 [95% CI, 2.29–4.18]; $P < 0.001$) were independently associated with 90-day mortality. In patients requiring mechanical ventilation, mortality rates ranged from 39% (no other risk factors for mortality) to 100% (four associated risk factors for mortality).

Conclusions: Most critically ill Allo-HSCT recipients survive their ICU stays, including those requiring mechanical ventilation, with an overall 90-day survival rate reaching 51.8%. A careful assessment of goals of care is required in patients with two or more risk factors for mortality.

Keywords: graft-versus-host disease; mechanical ventilation; shock; acute kidney injury; immunomodulation

10.1017/8491379 by Biblioteca IRCCS Istituto Oncologico Veneto - Pad

Sopravvivenza nel Paziente Critico (Coorte di 1.164 Casi)

51.8%

Sopravvivenza Globale a 90 Giorni

Mortalità in ICU contenuta al 26% (302 decessi su 1.164).

Superamento del Pessimismo Clinico

La maggior parte dei pazienti con allo-HSCT sopravvive alla degenza in Terapia Intensiva.

Supporti Vitali Erogati

Ventilazione meccanica invasiva (38%), vasopressori (41%), dialisi RRT (19%).

Traiettoria a Lungo Termine

Mortalità a 1 anno pari al 63% e a 3 anni al 70%, legata primariamente alla malattia di base.

....il paradigma cambia se però.....

⌚ Paradigm Shift in ICU Candidacy for Allogeneic Hematopoietic Stem Cell Transplantation: Who, When, and How Long?

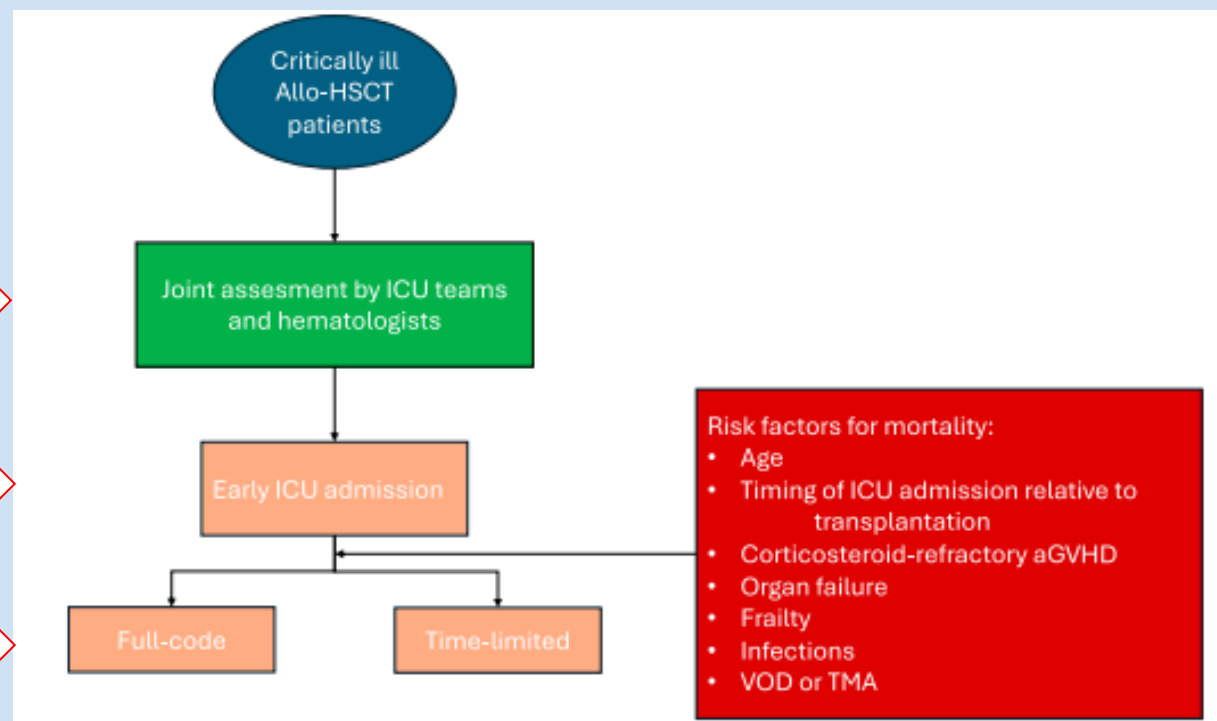
Who



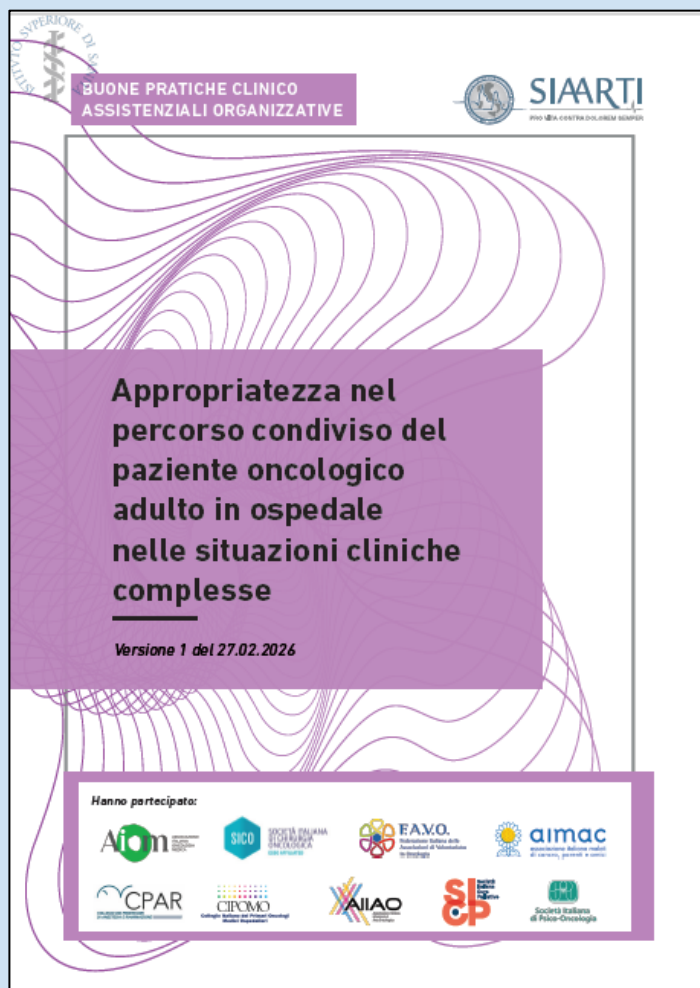
When



How Long



Livelli di Trattamento e Proporzionalità



Percorso di Escalation in Terapia Intensiva

1

Intercettazione

Score NEWS 2 seriale e rilevamento del deterioramento precoce.

Chart 1: The NEWS scoring system

Physiological parameter	3	2	1	Score 0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO ₂ Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO ₂ Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0						

NEW score	Clinical risk	Response
Aggregate score 0–4	Low	Ward-based response
Red score Score of 3 in any individual parameter	Low–medium	Urgent ward-based response*
Aggregate score 5–6	Medium	Key threshold for urgent response*
Aggregate score 7 or more	High	Urgent or emergency response**

TAKE-HOME MESSAGES

Tempestività, Multidisciplinarietà e Proporzionalità

1. Accesso Precoce in ICU: Intercettare il danno prima della triade letale ipotensione-ipossia-acidosi.

2. Condivisione Quotidiana: Confronto costante tra intensivista ed ematologo sul bilancio rischio-beneficio.

3. Flessibilità del Trial: Il Time-Limited Trial assicura intensità di cura senza accanimento terapeutico.





.....grazie per l'attenzione