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Impact of early ICU admission on outcome of critically ill and critically ill cancer patients: a systematic review and meta-analysis.

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Abstract

Objective: Prognostic impact of early ICU admission remains controversial. The aim of this review was to investigate the impact of early ICU admission in the general ICU population and in critically ill cancer patients and to report level of evidences of this later.

Methods: Systematic review and meta-analysis performed on articles published between 1970 and 2017. Two authors extracted data. Influence of early ICU admission on mortality is reported as Risk Ratio (95%CI) using both fixed and random-effects model.

Data Synthesis: For general ICU population, 31 studies reporting on 73,213 patients were included (including 66,797 patients with early ICU admission) and for critically ill cancer patients 14 studies reporting on 2,414 patients (including 1,272 with early ICU admission) were included.

Early ICU admission was associated with decreased mortality using a random effect model (RR 0.65; 95% confidence interval 0.58-0.73; $I^2=66\%$) in overall ICU population as in critically ill cancer patients (RR 0.69; 95% confidence interval 0.52-0.90; $I^2=85\%$).

To explore heterogeneity, a meta-regression was performed. Characteristics of the trials (prospective vs. retrospective, monocenter vs. multicenter) had no impact on findings. Publication after 2010 (median publication period) was associated with a lower effect of early ICU admission (estimate 0.37; 95%CI 0.14-0.60; $P=0.002$) in the general ICU population. A significant publication bias was observed.

Conclusion: Theses results suggest that early ICU admission is associated with decreased mortality in the general ICU population and in CICP. These results were however obtained from high risk of bias studies and a high heterogeneity was noted.

Systematic review registration: PROSPERO 2018 CRD42018094828

Introduction

Over the last two decades, survival of critical ill patients admitted in ICU has increased. Bellomo et al. found a decreased mortality in septic patients [1] and similar results were shown for patients requiring mechanical ventilation [2].

Similar trend was observed in critically ill cancer patients with septic shock [3] or acute respiratory distress syndrome (ARDS) [4]. More generally, in-ICU survival, in-hospital survival, 1-year survival of critically ill cancer patients was found to have increased [5], and this survival improvement remains after adjustment and in the subgroup of cancer patients [6].

Triage, ICU admission policy and early ICU admission strategy are among the many factors participating to this improved outcome. Thus, some studies suggested an increased survival in patients admitted early to the ICU both in the general population [7,8] and in immunocompromised patients [9,10].

In this systematic review of the literature, we sought to report the results of studies assessing relationship between early ICU admission and outcome in patients with and without underlying malignancy. Secondary endpoint was to assess reasons for delayed ICU admission.

Methods

Systematic review

This systematic review was performed according to PRISMA statements and PRISMA checklist is reported [11] (supplementary appendix, table S1).

The protocol of the systematic review was registered to the PROSPERO database (PROSPERO 2018 CRD42018094828 available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018094828).

Research strategy

A PubMed and Cochrane database search was performed using a 2-step process: 1/ search in general ICU patients: the following combination of Mesh terms and keywords: CRITICAL CARE and DELAY were introduced (figure 1) in patients without underlying malignancy ([NOT] NEOPLASM) 2/ in cancer patients with underlying malignancy ([AND] NEOPLASM) (figure 2).

Any reference cited in the analyzed articles and reviews were scrutinized and searched. Research limits were set between 1970 and July 2017.

Study population

Adult patients (>17 year) admitted to the ICU.

Time to ICU admission was defined by the estimation of time between hospital and ICU stay.

The outcomes of interest were hospital mortality or in its absence ICU and then 1-year mortality rates.

Study selection and inclusion exclusion criteria

Two investigators (YH and AM) screened titles and abstracts from all identified articles by both electronic and manual searches. Articles that did not meet the inclusion criteria were excluded. All remaining articles were obtained and full-text reviewed independently by YH and AM based on the following criteria: 1/ inclusion criteria confirmed; 2/ available data regarding delay between hospital and ICU admission; 3/ available data regarding mortality. For six articles, the two investigators disagreed on their reading of the reported data. Disagreements were resolved by discussion between investigators and a consensus was reached in every case. The flow diagram of the literature search is displayed in figure 1 for general ICU patients and figure 4 for critically ill cancer patients.

Data extraction

The texts of the potentially relevant studies were systematically evaluated. Data were extracted, synthesized, and analyzed. For each study, the following parameters were recorded: authors' names, date of publication, study design, journal publication, sample size and included subjects and RCTs, main results on association between delayed admission and mortality.

Early ICU admission definition

Early ICU admission was defined either according to authors' definitions or as the group with the lowest delay between first assessment and ICU admission.

Late ICU admission was defined according to authors' group or as the group with the longest delay between first assessment and ICU admission

When more than 2 groups (early and late ICU admission) were described by authors, groups with intermediate delay between ICU admission and outcome were excluded from the analysis.

Statistical analysis

Overall mortality of included patients and mortality in included studies are reported as medians (interquartile ranges). Publication bias was assessed by visually inspecting the funnel plot and summary estimates of relative risk and their 95% confidence interval were calculated using both fixed and random-effects model.

Cochran's Chi² test and I² test for heterogeneity were used to assess inter-study heterogeneity [12]. The Chi² test assesses whether observed differences among results are compatible with chance alone, and the I² describes the percentage of the variability in effect estimates that results from heterogeneity rather than from sampling error. An I² test for heterogeneity above 0.25 was considered to indicate moderate heterogeneity. Statistically significant heterogeneity was considered present at Chi² P < 0.10 and I² > 50%. All effect sizes with a p < .05 were considered significant. Tests were two-sided.

In way to explain heterogeneity, a meta-regression was performed.

Last, three sensitivity analyses were performed in way to assess impact of publication bias in the observed results using namely trim and fill method [13,14], Copas method [15] and Outcome Reporting bias method [16].

As sensitivity analysis an updated research was performed on February 2020.

All analyses were carried out with software R, version 3.4.4. The 'Meta', the 'metasens' and 'metaphor' packages were used to produce forest plots and run meta-regression and sensitivity analyses.

Results

General ICU population

Our initial search yielded 663 citations, of which 16 were excluded due to duplication and 576 were excluded as irrelevant for the scope of this review. All abstracts of the remaining records were carefully checked and 71 full text articles were scrutinized for further evaluation. Twelve studies were excluded as not focusing on critically ill patients or ICU setting, and 28 as not focusing on ICU admission process. Thirty-one studies were ultimately included in this analysis (**Figure 1**) [7,8,17–43].

Characteristics of the studies are reported in **table S2** and **table S3**.

These studies were published between 1990 and 2017. A total of 122, 475 patients were included in these studies, of whom 66,797 and 6,416 patients were considered as early ICU admission and delayed ICU admission respectively. For 49,262 patients, no classification was available between early or delayed ICU admission group. There were 14 prospective studies, every of them being cohort studies. The majority of the studies (n=23, 74%) had a monocentric design.

In the general ICU population early ICU admission was associated with decreased mortality with risk ratio of 0.66 [95%CI 0.59-0.74] while using fixed effect model and 0.70 [95%CI 0.67-0.72] while using random effect model. Significant heterogeneity was noted ($I^2=66%$) (**Figure 3**).

The funnel plot shown in **Figure S1** and linear regression test for funnel plot asymmetry did not suggest any publication bias.

Critically Ill cancer patients

Our initial search yielded 932 citations, of which 24 were excluded due to duplication and 865 were excluded as irrelevant for the scope of this review. All abstracts of the remaining records were carefully checked and 43 full text articles were scrutinized for further evaluation. Fifteen studies were excluded as not focusing onco-hematology population, eleven studies without assessment on timing of ICU admission and 4 studies were didactic review (**Figure 2**) [9,10,40,44–54].

Characteristics of the studies are reported in **table S4** and **table S5**. These studies were published between 1998 and 2017. A total of 12,751 patients were included in these studies, including: 1272 patients considered as early ICU admission and 1142 considered as delayed ICU admission. For 10,337 patients, no classification was available between early or delayed ICU admission. Overall, 8 of these studies (62%) were prospective, 7 (50%) were monocentric studies and none was randomized.

In this subset of patients, early ICU admission was associated with decreased mortality with risk ratio of 0.69 [95%CI 0.62-0.76] while using fixed effect model and 0.69 [95%CI 0.52-0.9] while using random effect model. Significant heterogeneity was noted ($I^2=80\%$) (**Figure 5**).

The funnel plot shown in **Figure S2** and linear regression test for funnel plot asymmetry did not suggest any publication bias.

Meta-regression and sensitivity analysis.

In order to explain the vast heterogeneity observed in both meta-analyses, meta-regressions and sensitivity analyses were performed.

In the general ICU population, characteristics of the trials (prospective vs. retrospective, monocenter vs. multicenter) had no impact on findings. **However, publication after 2010 (median) was associated with a lower effect of early admission (log risk-ratio of early ICU**

admission benefit vs. before 2010: 0.33; 95%CI [0.1-0.56]; P=0.005). Despite this effect, protective influence of early ICU admission remained significant during both study periods (risk ratio of 0.54 [95%CI 0.59-0.74] in studies published before 2010 vs. risk ratio of 0.77 [95%CI 0.70-0.84]).

In the onco-hematological patients, characteristics of the trials (prospective vs. retrospective, monocenter vs. multicenter) and year of publication had no impact on findings.

In the general ICU population, results were unchanged in sensitivity analyses used to adjust for funnel plot outlier (Trim and fill analysis and Copas methods) or analysis for Outcome Reporting Bias (supplementary appendix, **Table S6**).

In the Onco-Hematological ICU population, neither Copas methods nor sensitivity analysis for Outcome Reporting Bias, changed results (supplementary appendix, **Table S7**). Trim and fill method to adjust for funnel plot outlier led absence of impact of early ICU admission on outcome (OR 0.84; 95%CI [0.64-1.10]) (supplementary appendix, **Table S7**).

Last, an updated analysis was performed on February 2020 as sensitivity analysis. A single study was found relevant for this meta-analysis in the general ICU population. Results of the updated analysis were unchanged and are reported in supplementary appendix (**Figure S3** and **Figure S4**). No study was found relevant in the Onco-Hematological ICU group.

Discussion

To the best of our knowledge, this is the first systematic review to address the relationship between time to ICU admission and outcomes with a special focus for critically ill cancer patients. Delayed ICU admission is believed to be associated with higher mortality or unfavorable outcomes. This assumption is however poorly supported by high degree evidences, except in very specific conditions. Hence, fast implementation of treatment is a standard of care for septic patients [55], and delay between event and management (treatment or transfer to an intensive care unit) well validated in patients with myocardial infarction [56], stroke [57] or major trauma [58]. According to our results, a shorter delay between hospitalization and ICU admission is associated with lower mortality in the general ICU population and in critically ill cancer patients.

In general ICU population, a large multicentric cohort [7] published in 2007 showed a better outcome for patients considered with an early ICU admission (emergency department boarding < 6 hrs.): a decrease in hospital length of stay, a decrease in ICU and in hospital mortality. In a recent retrospective study [40], delayed ICU admission (waiting > 4 hours in emergency department) affected the outcomes of 21-ventilator-day mortality and prolonged hospital stay. Some studies however show inconsistent results and O'Callaghan [34] showed no difference for ICU length of stay or in ICU mortality in a retrospective study between delay (> 3hrs from referral to admission) or no delay-group. As underlined by this review, difference in definition and publication bias in favor of positive study publication may explain these discrepant results.

In critically ill cancer patients, results are more consistent, a single study failing to demonstrate benefit of early ICU admission [53]. This study however included a limited sample size, and secondary endpoints were in favor of early ICU admission. More importantly, studies in this setting, concurrently suggested difficulty to assess patients'

severity, a high rate of clinical worsening after initial assessment by physician and a high mortality in patients initially considered too well to benefit from ICU admission and requiring subsequent ICU admission [59]. For acute respiratory failure patients [9], a delayed ICU admission (> 2 days between respiratory symptoms onset and ICU admission) was an independent predictor of day-28 mortality. A prospective cohort showed [52] an increase of long-term outcome in early intervention group after clinical derangement on general wards (< 1.5 hours) and reduced 1-year mortality compared to late intervention. However, no high degree of evidence study was recorded, raising doubt as regard to causality of the findings in this setting.

Several limits deserve to be noted. First, both results in general ICU population and critically ill cancer patients reported a high heterogeneity across studies. The performed meta-regression failed to identify characteristics of the studies as associated with the observed effect. Hence, only date of publication was found to be associated with a lower effect for studies published more recently. Another limit is related to definition of early ICU admission definition which was inconsistent across studies, mainly relying on time between hospital or Emergency Department and ICU admission. Another limit is that most of the reported studies being low level evidence studies, patient characteristics and study design varying across publication. Thus, clustering effect related to unrecorded variable may explain timing of ICU admission, these variables ranging from patients' severity, disease course, ICU admission policy, every of which may have influenced our findings. **For example, availability of ICU beds, influence of rapid response team, health care system organization and their interaction with prompt ICU admission or outcome were infrequently assessed [51] and could not be specifically evaluated in this study. In the same line, reason for ICU admission may influence timing of ICU admission and therefore findings. Despite our best efforts, it was impossible to adjust for this limit in this meta-analysis on aggregated data. Underlying reason for ICU**

admission may therefore act as a confounder which may have influenced our findings. Moreover, timing of ICU admission may be viewed as a continuous variable rather than a binary variable. Additional studies may be required to assess whether timing as continuous variable may influence outcome and if patients' case-mix may interact with this association, different case-mix being potentially associated with different patterns. Thus, despite these encouraging results, benefit of early ICU admission needs to be validated by low risk of bias studies.

This systematic review suggest that early ICU admission is associated with decreased mortality in the general ICU population and in Critically ill Cancer Patients. These data however arise from studies at high risk of bias, and a high heterogeneity was noted. Additional studies are required to confirm potential benefit of multifaceted strategies aiming to decrease delay between early sign of organ dysfunction and ICU admission, to assess impact of such strategy in real life practice and on hard clinical endpoints, while taking into account patients' and patients' next of kin reported outcome on one hand and cost-benefit ratio for the health care system on the other.

DISCLOSURES

M. Darmon has received fees from Sanofi MSD, Gilead-Kite and Astellas, and research support from MSD.

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The other authors declare having no conflict of interest related to this manuscript.

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Figures captions

Figure 1 – Flow chart of study selection for studies in general ICU population

Figure 2 – Flow chart of study selection for studies in critically ill cancer patients.

Figure 3 – Impact of early ICU admission in the general ICU population.

Figure 4 – Impact of early ICU admission in critically ill cancer patients.

Identification

Records identified through database searching PubMed (n= 655), integrative literature review (n= 8)

Screening

663 studies

Records Exluded n= 592

Eligibility

Full-text articles assessed for eligibility (n = 71)

Full-text articles excluded, with reasons : not focalized on ICU (n = 12), not focusing on ICU admission process (n = 28)

Included

31 studies

Identification

Records identified through database searching PubMed and handsearch (n=932)

screening

932 studies

Eligibility

Full-text articles assessed for eligibility (n=43)

Included

13 studies

Full-text articles excluded, with reasons : focus not on cancer patients (n=15), delay for ICU admission patient not reported (n=11), didactic review (n=4)

Study	Experimental		Control		Weight (fixed)	Weight (random)	Risk Ratio MH, Fixed + Random, 95% CI	Risk Ratio MH, Fixed + Random, 95% CI
	Events	Total	Events	Total				
Augustin , 2017	31	137	37	150	1.1%	4.1%	0.92 [0.60, 1.39]	
Bing-Hua , 2014	140	2094	16	185	0.9%	3.3%	0.77 [0.47, 1.27]	
Cardoso, 2011	47	125	138	276	2.6%	6.4%	0.75 [0.58, 0.97]	
Chalfin , 2007	6358	49286	180	1036	10.7%	8.6%	0.74 [0.65, 0.85]	
Chiavone, 2005	6	23	38	71	0.6%	1.9%	0.49 [0.24, 1.00]	
Garrouste Orgeas, 2005	113	382	7	30	0.4%	2.1%	1.27 [0.65, 2.47]	
Intas, 2012	28	60	88	140	1.6%	5.7%	0.74 [0.55, 1.00]	
Khan, 2016	34	164	44	161	1.3%	4.4%	0.76 [0.51, 1.12]	
Landoni, 2012	6	15	9	15	0.3%	1.8%	0.67 [0.32, 1.40]	
Louriz, 2012	37	110	64	146	1.7%	5.4%	0.77 [0.56, 1.06]	
Molina, 2014	109	490	73	208	3.1%	6.5%	0.63 [0.49, 0.81]	
Naval, 2009	17	77	11	48	0.4%	2.1%	0.96 [0.49, 1.88]	
O'Callaghan, 2012	353	1460	40	149	2.2%	6.0%	0.90 [0.68, 1.19]	
Parkhe, 2002	9	99	8	23	0.4%	1.5%	0.26 [0.11, 0.60]	
Phua, 2010	11	54	25	49	0.8%	2.5%	0.40 [0.22, 0.72]	
Rapoport, 1990	146	696	141	304	5.9%	7.6%	0.45 [0.37, 0.55]	
Renaud, 2012	26	199	28	144	1.0%	3.3%	0.67 [0.41, 1.10]	
Restrepo, 2010	33	142	9	19	0.5%	2.8%	0.49 [0.28, 0.86]	
Robert, 2012	308	1131	64	192	3.3%	7.0%	0.82 [0.65, 1.02]	
Simpson, 2005	2930	9389	1268	2879	58.8%	9.6%	0.71 [0.67, 0.75]	
Sprung, 1999	41	290	11	31	0.6%	2.8%	0.40 [0.23, 0.69]	
Tilluckdharry, 2005	28	339	28	104	1.3%	3.5%	0.31 [0.19, 0.49]	
Young, 2003	4	35	23	56	0.5%	1.1%	0.28 [0.11, 0.74]	

Total (fixed effect, 95% CI) **66797** **6416** **100.0%** -- **0.70 [0.67, 0.72]**
Total (random effects, 95% CI) -- **100.0%** **0.66 [0.59, 0.74]**

Heterogeneity: Tau² = 0.03; Chi² = 64.07, df = 22 (P < 0.01); I² = 66%

Test for overall effect (fixed effect): Z = -17.35 (P < 0.01)

Test for overall effect (random effects): Z = -7.43 (P < 0.01)



