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Impact of early ICU admission for critically ill cancer patients: Post-hoc analysis of a prospective multicenter multinational dataset.

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ABSTRACT

Objectives: Early intensive care unit (ICU) admission, in Critically Ill Cancer Patients (CICP), is believed to have contributed to the prognostic improvement of critically ill cancer patients. The primary objective of this study was to assess the association between early ICU admission and hospital mortality in CICP.
Design: Retrospective analysis of a prospective multicenter dataset. Early admission was defined as admission in the ICU < 24 h of hospital admission. We assessed the association between early ICU admission and hospital mortality in CICP via survival analysis and propensity score matching.
Results: Of the 1011patients in our cohort, 1005 had data available regarding ICU admission timing and were included. Overall, early ICU admission occurred in 455 patients (45.3%). Crude hospital mortality in patients with early and delayed ICU admission was 33.6% ($n = 153$) vs. 43.1% ($n = 237$), respectively ($P = 0.02$). After adjustment for confounders, early compared to late ICU admission was not associated with hospital mortality (HR 0.92; 95%CI 0.76–1.11). After propensity score matching, hospital mortality did not differ between patients with early (35.2%) and late (40.6%) ICU admission ($P = 0.13$). In the matched cohort, early ICU admission was not associated with mortality after adjustment on SOFA score (HR 0.89; 95%CI 0.71–1.12). Similar results were obtained after adjustment for center effect.
Conclusion: In this cohort, early ICU admission was not associated with a better outcome after adjustment for confounder and center effect. The uncertainty with regard to the beneficial effect of early ICU on hospital mortality suggests the need for an interventional study.

1. Introduction

Cancer is a major public health problem worldwide, and is one of the most common cause of death in the general population and is the first cause in patients over 40 years old [1,2]. Many cancer patients require admission in intensive care unit (ICU) for life-threatening events. These patients may experience complications directly or indirectly related to the underlying malignancy and its management. Increasing incidence of cancer, introduction of new treatments with specific toxicity [3], along with increasing patients survival is likely to increase the incidence of cancer patients requiring ICU admission [4]. Currently, approximatively 15% of ICU admissions occur in cancer patients [5].

During the last two decades, survival of cancer patients has progressively increased [6-8]. Among factors that may have improved

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outcome, changes in therapeutic options, including intensive chemotherapy [9], biotherapy, targeted therapy [10,11] and cellular therapies with CAR-T cells [12] have considerably improved chances to obtain event free survival [13,14]. When ICU admission is required, mortality remains high despite progressive improvement over the last decades [7]. Optimizing organization and management strategies may further improve critically ill cancer patients' outcome [15,16].

Early ICU admission has been associated with cancer patients survival with organ failure [15,17]. In this line, triage decision for ICU admission is highly dependent from physician appreciation which was found to be poorly reliable in evaluating risks of clinical deterioration [18]. Conversely, delay to admit patients with new organ dysfunction was found to be associated with a progressive, time-dependent, worsening of the outcome [19]. Despite statistical association, consistent results, and steadily increase in mortality with increase delay in admitting patients, these results are based upon low level evidences studies, influenced by clustering effect that may have affected association between timing of ICU admission and outcome [20].

The primary objective of this study was to investigate whether early ICU admission is associated with lower hospital mortality in critically ill cancer patient.

2. Patients and methods

2.1. Study population

We performed a retrospective analysis of prospectively collected dataset [21]. Briefly, adult patients with underlying hematological malignancy and admitted to the ICU were prospectively included from 2010 to 2012 in 17 university or university-affiliated centres in France and Belgium belonging to the GRRROH research network. In every centre, a senior intensivist and a senior hematologist were available around the clock and made triage decisions together. Participating ICUs re closed ICUs with high intensivist staffing, and with a high critically ill cancer patients' volume. The appropriate ethics committees approved this study [21].

2.2. Definitions

Data were collected prospectively.

Newly diagnosed hematological malignancies were defined as diagnosed within the past 4 weeks.

The **Sepsis-Related Organ Failure Assessment (SOFA)** score was computed at admission and daily throughout the patient's stay in the ICU; this score provides an estimate of the risk of death based on organ dysfunction [22].

The **Performans Status** [23] and **Charlson comorbidity index** [24] were determined at ICU admission. Both leukemia and lymphoma are already part of the Charlson comorbidity index [24].

Reasons for ICU admission were recorded based on the main symptoms at ICU admission. Acute respiratory failure was defined as oxygen saturation less than 90% or PaO2 less than 60 mmHg on room air combined with severe dyspnea at rest with an inability to speak in sentences or a respiratory rate greater than 30 breaths per minute or clinical signs of respiratory distress [25]. Shock was defined as previously reported [17]. Life-sustaining therapies, renal replacement therapy (RRT), anti-infectious agents, prophylactic treatments, urate oxidase use, and diagnostic procedures were administered at the discretion of the attending intensivists, who followed best clinical practice and guidelines. Chemotherapy, corticosteroids, hematopoietic growth factors, immunosuppressive drugs, and other cancer-related treatments were prescribed by the hematologist in charge of each patient in accordance with institutional guidelines. Tumor lysis syndrome was defined according to the recent guidelines [26].

Etiologic diagnoses were made by consensus by the intensivists, hematologists, and consultants, according to recent definitions [21]. In particular, etiologies of pulmonary involvement were diagnosed based on predefined criteria [25]; for possible or probable invasive pulmonary aspergillosis, the most recent definitions were used [27].

Direct admission was defined by an ICU admission directly from emergency department. **Early ICU admission** was defined as ICU admission occurring within 24 h of hospitalization, late ICU admission by ICU admission occurring more than 1 day following hospital admission.

Senior physician was defined by experience of physician in charge of triage (senior physician, fellow or resident).

2.3. Statistical analysis

Results are described as medians and interquartile ranges (IQR) for quantitative variables and numbers and percentages for qualitative

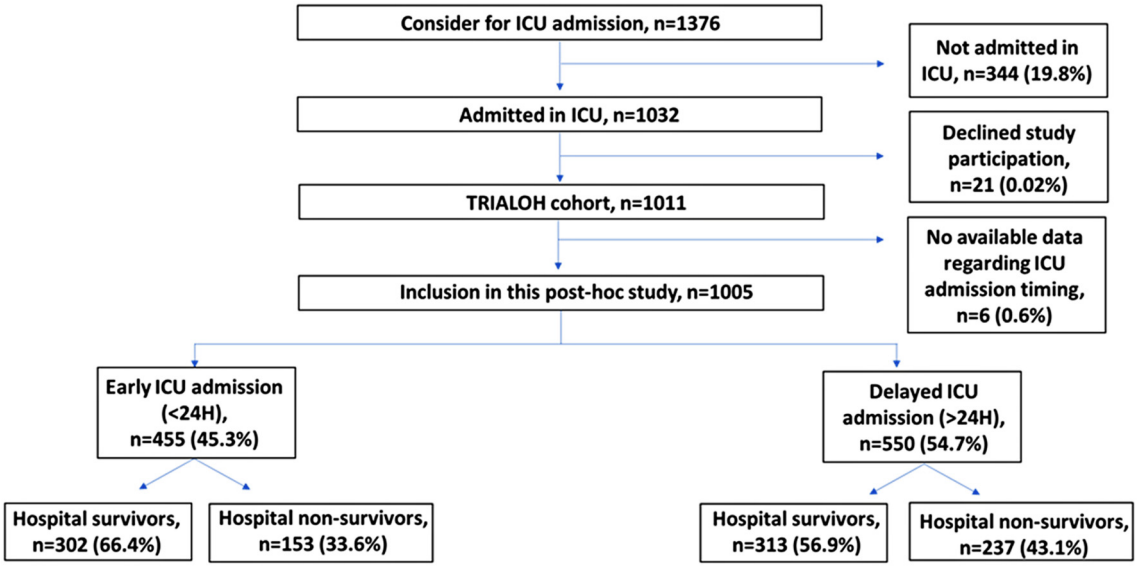

Fig. 1. Flow chart of included patients.

variables. We used a non-parametric Wilcoxon tests and Fisher exact tests for baseline univariate comparisons between two groups.

Cox models were performed to identify factors associated with hospital mortality and early ICU admission. Logistic models were backward condition model according to *P* value considering entry P value of 0.2 and critical removal P value of 0.1. It was a priori decided to force should early ICU admission be not selected to force this variable in the final model. Proportional hazard assumption, linearity of continuous variables and role of outliers were checked in every of the performed models.

Last, in way to take into account factors associated with early admission and potentially confounding for mortality, a sensitivity analysis was performed, including a propensity score matching according to nearest neighbour method. Propensity score was derived from logistic regression including variables independently associated with early ICU admission and associated with hospital mortality with a *P* value of 0.2 or less. Adequacy of matching was evaluated using pre and post matching population characteristics, propensity score in overall and matched population, and standardized mean difference across characteristics used to match patients. Impact of early ICU admission was then assessed in the matched population before adjustment and after adjustment for variables remaining unbalanced using Cox model.

Two sensitivity analyses were performed:

First, impact of early ICU admission was assessed in specific subgroups, namely patients admitted with an acute respiratory failure. Similar to the main analysis, raw impact of early admission, adjusted impact and influence in a matched cohort were assessed.

Last, Centre effect was assessed using penalized Cox model, variables previously selected being entered the model with centre as frailty term, then in a matched cohort, where centre effect was included as a matching variable.

Survival curves were constructed according to the Kaplan–Meier method. Comparison according to timing of admission was performed using the log-rank test.

All tests were two-sided, and *P* values less than 0.05 were considered significant. Analyses were done using *R* software version 4.3.4 (R Project for Statistical Computing, Wien, Austria) and with 'Survival' and 'MatchIt' packages.

3. Results

3.1. Patients' characteristics

Of the 1011 patients included in the initial cohort, data related to ICU admission were available in 1005 patients ultimately included in this sub-study (Fig. 1, Table 1, Table S1).

Main characteristics of the patients are reported in Table 1. Overall, 611 patients (60.8%) were of male gender and median age was of 60 (49–70) years. Median SOFA score at ICU admission was 6 (3–9). Median Charlson's comorbidity index was 4 (2–5) and 196 patients (19.5%) had a poor Performans Status (bedridden/ completely disabled). Underlying malignancy was an acute leukemia in 345 patients (34.3%), a Non-Hodkin's lymphoma in 318 patients (31.6%), and a Myeloma in 126 (12.5%). Two hundred and thirty-two patients (23.1%) had partial or complete remission and 144 were allogeneic stem cell transplant recipients (14.3%).

Main reasons for ICU admission were acute respiratory failure in 371 patients (36.9%), shock in 172 (17.12%), sepsis in 104 (10.4%), acute kidney injury in 68 (6.8%), coma in 225 (22.3%) and specific organ infiltration and need for cancer chemotherapy along with organ support in 70 (6.9%).

3.2. Timing of ICU admission

Overall, 267 patients (26.6%) were directly admitted to the ICU and ICU admission occurred in median 4 days [1-6] after hospital admission. According to our definition, 455 patients (45.3%) were classified as admitted early in the ICU and 550 patients (54,7%) were consider as having a delayed ICU admission (Fig. 1). Half (51%, $n = 232$) of the patients with early ICU admission were directly admitted in the ICU. Patients were admitted after a median of 0 days [0–0] in the early ICU admission group and after a median of 9 days [3-20] in the delayed ICU admission group.

As listed in Table 1, patients with early ICU admission were more frequently male gender, less frequently allogeneic stem cell transplant recipients or in complete remission and had a higher rate of newly diagnosed malignancy. Patients with delayed ICU admission had poorer performance status. Beside patients' characteristics, senior involvement in ICU transfer was associated with early ICU admission. At ICU admission SOFA score was similar across groups.

Table 1
Patient's characteristics according to Early ICU admission or Delayed ICU admission.

	Early ICU admission n (%)	Delayed ICU admission n (%)	*P*-value
	455 (45.3%)	550 (54.7%)	
Age (years)	60 [47–70]	60 [50–69]	0.88
Male gender	290 (63.7%)	321 (58.4%)	0.09
Hospital to ICU admission (days)	0[0–0]	9 [3–20]	<0.001
n call to the ICU before admission>1	24 (5.3%)	80 (14.5%)	<0.001
Physician involved in ICU transfer		332 (62.3%)	<0.001
Senior physician	318 (71.1%)	90 (16.9%)	
Fellow	79 (17.7%)	111 (20.8%)	
Resident	50 (11.2%)		
Direct admission*	232 (51%)	35 (6.4%)	<0.001
Surgical Patient	34 (7.5%)	57 (10.4%)	0.14
Underlying malignancy			0.06
Non hodgkin's lymphoma	147	171	
Acute leukemia	137	208	
Myeloma	66	60	
Chronic lymphocytic leukemia	40	36	
Other	65	75	
BMT/stem cell transplantation			
Autologous	53 (11.7%)	90 (16.5%)	0.04
Allogeneic	50 (11%)	94 (17.2%)	0.007
Malignancy status at ICU admission			< 0.001
Newly diagnosed malignancy	132 (29.0%)	101 (18.3%)	
No remission	158 (34.7%)	241 (43.8%)	
Partial or complete remission	100 (22.0%)	132 (24.0%)	
Unknown/not evaluable	65 (14.3%)	76 (13.8%)	
Neutropenia at ICU admission			
Neutropenia	50 (11.1%)	42 (7.8%)	0.08
Within 48 h of Neutropenia recovery	19 (4.2%)	66 (12.1%)	< 0.001
Experience of ICU physisician involved in ICU triage			< 0.001
Resident	50 (11.2%)	111 (20.8%)	
Fellow	79 (17.7%)	90 (16.9%)	
Senior	318 (71.1%)	332 (62.3%)	
Performans status (PS)			
Poor performans status *	65 (13.4%)	135 (24.5%)	< 0.001
SOFA score*	6 [3–9]	6[3–9]	0.77
Full Code at ICU admission	437 (96.0%)	531 (96.5%)	0.80
Life-sustaining therapies at ICU admission			
Vasoactive drugs	153 (33.7%)	170 (30.9%)	0.38
Invasive mechanical ventilation	133 (29.2%)	155 (28.2%)	0.73
NIMV*	54 (11.9%)	111 (20.2%)	<0.001
RRT*	64 (14.1%)	49 (8.9%)	0.009
Outcome			
ICU mortality	118 (25.9%)	160 (29.1%)	0.30
Hospital mortality	153 (33.6%)	237 (43.1%)	0.02

*Direct ICU admission: Direct admission or admission from Emergency Department (delay 1 days [0–4] since hospital admission); Poor performance Status: bedridden or completely disabled; NIMV: noninvasive mechanical ventilation; RRT: renal replacement therapy. SOFA score was assessed at ICU admission.

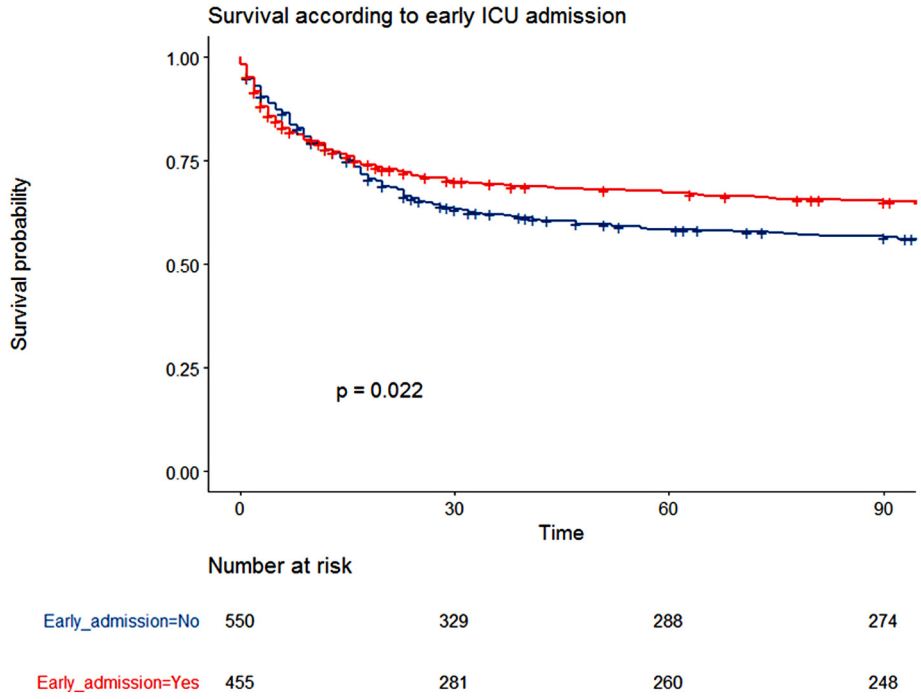

Fig. 2. Cumulative survival according to timing of ICU admission in the whole study population. Early ICU admission (red) is compared to delayed ICU admission (blue) and survival is compared using log-rank test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Factors independently associated with early ICU admission are reported table S2. Overall, poor Performans Status (OR 0.47; 95%CI 0.32–0.68), previous allogeneic stem cell transplantation (OR 0.65; 95%CI 0.42–1.01), resident as main interlocutor during triage procedure (OR 0.46 vs. senior physician; 95%CI 0.3–0.7) and neutropenia recovery at ICU admission (OR 0.29; 95%CI 0.16–0.52) were associated with delayed ICU admission.

3.3. Prognostic impact of early ICU admission in entire study population

Hospital mortality was 38.8% ($n = 390$) including 153 and 237 patients with early and late ICU admission respectively (33.1% vs. 42.1%, $P = 0.02$) (Fig. 2, Table S1).

After adjustment for confounders, age (HR 1.01 per year; 95%CI 1.01–1.02), allogeneic stem cell transplantation (HR 1.54; 95%CI

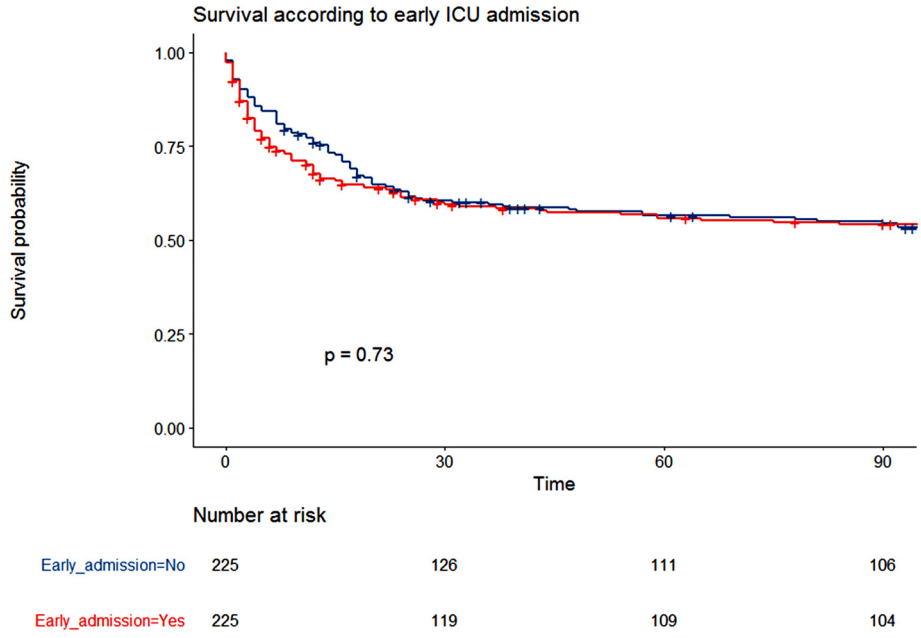

Fig. 3. Cumulative survival according to timing of ICU admission in the matched cohort and after adjustment for SOFA score. Early ICU admission (red) is compared to delayed ICU admission (blue) and survival is compared using log-rank test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.20–1.98), hepatic comorbidity (HR 1.42; 95%CI 1.08–1.87), poor Performans Status (HR 1.38; 95%CI 1.12–1.72) and a higher severity as assessed by SOFA score (HR per point 1.14; 95%CI 1.12–1.17) were associated with poor outcome. However, Early ICU admission was not selected in the final model, and when forced in this later was neither significant nor not statistically significantly associated with changes in observed association with hospital mortality (HR 0.92; 95%CI 0.76–1.11).

3.4. Prognostic impact of early ICU admission after matching

In order to further assess impact of early admission while taking into account factors associated with early ICU admission, a propensity score matching was performed. Underlying hematological malignancy status, Performans Status and allogeneic stem cell transplantation were included in the propensity score. Patients' characteristics before and after matching, along with standardized mean difference are reported in table S3 (supplementary appendix). Propensity scores distribution before and after matching are reported in figs. S1 and S2 (supplementary appendix).

After matching 389 patients with early ICU admission and 389 patients delayed ICU admission were compared (Table S3). Hospital mortality was similar across patients' group (35.2% and 40.6% respectively for patients with early and delayed admission, $P = 0.13$). After adjustment for patients' severity according to SOFA score, early admission was not associated with hospital mortality (HR 0.89; 95%CI 0.71–1.12). Overall survival according to early admission group is reported in Fig. 3.

3.5. Sensitivity analysis

First, in the subset of patients with acute respiratory failure ($n = 628$), early ICU admission failed to be associated with outcome (Table S4, Fig. S3 and S4).

When center effect was taken into account, in the whole cohort or in the matched cohort, early ICU admission failed to be associated with outcome (Table S5).

4. Discussion

This study is, to the best of our knowledge, the largest to assess the impact of early ICU admission on critically ill cancer patients' outcome. After careful matching on risk factors of early ICU admission and on variables associated with outcome, early ICU admission failed to be associated with outcome. Our results may suggest that association between timing of ICU-admission and outcome were related to confounding factors.

Overall outcome of critically ill onco-hematological patients has increased during the last decades [6,7] due to progress in cancer therapy, change in ICU admission policy [15,28], increasing number and performance of non-invasive diagnosis strategies available [25] and improvement of critical care [29]. Despite these progresses, an increasing number of cancer patients requires intensive care admission as consequences of new, efficient, but potentially toxic therapeutic strategies [3,12].

Several studies suggested a beneficial effect of early ICU admission strategy [18,30-35]. Early ICU admission however differed across these studies from a few hours following physiological disturbances to several days following hospital admission [32,34-36]. Studied population also differed including multiple myeloma patients [31], cancer patients with acute respiratory failure [32], overall onco-hematological patients assessed by an outreach team [35], high grade hematological malignancy [34], or shock patients [36].

These studies were consistent with studies suggesting a misperception of patients' severity by physicians. Indeed Thiéry et al. [19] showed an increased mortality among patients considered too well to benefit from ICU admission and subsequently requiring ICU admission due to clinical deterioration. If most of the studies suggested delayed ICU admission to be associated with poor outcome, this association may however partly reflect prognosis impact of clinical worsening or lack of improvement [20]. In our study, no benefit from early ICU admission was observed. These results persisted after adjustment for confounders and matching for factors associated with early ICU admission, suggesting confounders to participate to the previously observed benefit.

Our study has some limits that should temper our finding. First, every patient was admitted in high volume centers, used to care onco-hematological patients and with presence of a hematologist or an oncologist 24/7. This may reflect a bias in ICU admission policy in favor of early ICU admission. This may also decrease external validity of our finding which may not hold in low volume centers. In this line, patients were admitted in the ICU nearly a decade ago and practice may have changed limiting interpretation of our findings. In addition, although we adjusted on available risk factors of early ICU admission and of poor outcome, some variables, including variables associated with clustering effect were not available and not adjusted for. Thus, allocation bias, including unmeasured confounders that may have influence timing of ICU admission, might have influenced our results. For example, a higher rate of patients required ventilatory support (invasive and/or non-invasive ventilation) in the late ICU admission group which may reflect either a higher respiratory severity or higher rate of respiratory failure in this group. Thirdly, definition of early or delayed ICU admission was defined by a delay between hospital admission and ICU admission of 24 h. Although this delay is in line with definitions found in literature, it may be viewed as arbitrary and may differ from delay between onset of the acute condition and ICU admission. Last, our study may either have lacked statistical power to demonstrate benefits from early ICU admission.

In a large prospectively collected cohort, we failed to demonstrate protective effect of early ICU admission. Our negative results suggest that a trial comparing usual practices to early ICU admission strategy in caring for onco-hematological patients with organ failure might be required. Only such a trial may help in delineating objectively influence of early ICU admission on outcome, underline resources consumption associated with such strategy, and determine cost-effectiveness in real life practice.

Authors' statement

YH participated study Conceptualization, Data curation, Methodology, Data Analysis, Writing the original draft and reviewing & editing the final draft.

AK participated study Data acquisition, Investigation, Data interpretation, and reviewing & editing the final draft.

RL participated study Data acquisition, Investigation, Data interpretation, and reviewing & editing the final draft.

DM participated study Data acquisition, Investigation, Data interpretation, and reviewing & editing the final draft.

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APM participated study Data acquisition, Investigation, Data interpretation, and reviewing & editing the final draft.

DB participated study Data acquisition, Investigation, Data interpretation, and reviewing & editing the final draft.

VL participated study Data acquisition, Investigation, Data interpretation, and reviewing & editing the final draft.

EA participated study Conceptualization, Supervision, Methodology, Project administration, Data Analysis, Writing the original draft and reviewing & editing the final draft.

MD participated study Conceptualization, Data curation, Investigation, Methodology, Project administration, Data Analysis, Writing the original draft and reviewing & editing the final draft.

YH and MD had access to full data and take responsibility for content of the manuscript.

Disclosures

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

E. Azoulay has received fees for lectures from Gilead, Pfizer, Baxter and Alexion. His research group has been supported by Ablynx, Ficher & Payckle, Jazz Pharma, and MSD.

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.10.022.

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