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ORIGINAL ARTICLE

Predictors, prognosis and costs of prolonged intensive care unit stay after surgery for type A aortic dissection

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ABSTRACT

BACKGROUND: The outcomes after prolonged treatment in the intensive care unit (ICU) after surgery for Stanford type A aortic dissection (TAAD) have not been previously investigated.

METHODS: This analysis included 3538 patients from a multicenter study who underwent surgery for acute TAAD and were admitted to the cardiac surgical ICU.

RESULTS: The mean length of stay in the cardiac surgical ICU was 9.9±9.5 days. The mean overall costs of treatment in the cardiac surgical ICU 24086±32084 €. In-hospital mortality was 14.8% and 5-year mortality was 30.5%. Adjusted analyses showed that prolonged ICU stay was associated with significantly lower risk of in-hospital mortality (adjusted OR 0.971, 95%CI 0.959-0.982), and of five-year mortality (adjusted OR 0.970, 95%CI 0.962-0.977), respectively. Propensity score matching analysis yielded 870 pairs of patients with short ICU stay (2-5 days) and long ICU stay (>5 days) with balanced baseline, operative and postoperative variables. Patients with prolonged ICU stay (>5 days) had significantly lower in-hospital mortality (8.9% *vs.* 17.4%, <0.001) and 5-year mortality (28.2% *vs.* 30.7%, P=0.007) compared to patients with short ICU-stay (2-5 days).

CONCLUSIONS: Prolonged ICU stay was common after surgery for acute TAAD. However, when adjusted for multiple baseline and operative variables as well as adverse postoperative events and the cluster effect of hospitals, it was associated with favorable survival up to 5 years after surgery.

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KEY WORDS: Aortic dissection; Intensive care unit; Hospital costs.

Surgery for Stanford type A aortic dissection (TAAD) is associated with significant risks of early mortality and major postoperative adverse events.[1] TAAD patients may die in the operating room or shortly after because of uncontrollable bleeding and/or acute heart failure, while many patients with significant pre- and postoperative complications related to aortic dissection or secondary to complex surgical repair may require prolonged treatment in the cardiac surgical intensive care unit (ICU). No study has previously evaluated the prognostic impact of ICU treatment on these patients and only a few studies focused on the identification of risk factors associated with prolonged ICU stay.[2-4] Predictors, prognosis, and costs of prolonged ICU treatment after surgery for acute TAAD have been investigated in the present study.

Materials and methods

Study population

The European Registry of TAAD (ERTAAD)[5] was a retrospective, multicenter study including consecutive patients who underwent surgery for acute TAAD at 17 centers of cardiac surgery in eight European countries from January 2005 to March 2021 (Supplementary Digital Material 1: Supplementary Table I). The Ethical Review Board of the Helsinki University Hospital, Finland (April 21, 2021, diary no. HUS/237/2021) and the Ethical Review Board of each participating hospital approved this study. The requirement for informed consent was waived because of the retrospective nature of this study. In this study we followed the STROBE guidelines for cohort studies.[6] The study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

Patients who fulfilled the following inclusion criteria were included in this registry: TAAD with symptoms arisen within seven days before surgery; patients >18 years old; primary surgery for acute TAAD; any concomitant major cardiac surgical procedure.[5] The exclusion criteria of the registry were the following: prior surgical or endovascular procedure for TAAD; retrograde TAAD; concomitant endocarditis; TAAD related to trauma.[5]

Patients who died in the operating room were excluded from this analysis. Patients with complete data on the length of stay in the cardiac surgery ICU were the subjects of the present analysis. The length of cardiac surgical ICU was calculated considering any readmission to the ICU.

Outcomes

The primary outcome of this study was in-hospital mortality, *i.e.* all-cause mortality occurred during the index hospitalization. The secondary outcome was five-year all-cause mortality. The length of stay in the ICU was a secondary outcome as well as covariate of main interest of this analysis. Early postoperative adverse events considered in this analysis were complications occurred during the index hospitalization. Death occurred in the ICU was not considered an outcome measure of this study because we expected that, in a few instances, patients with intractable complications might have been transferred to the ward after treatment withdrawal. Data on the date of death were collected retrospectively from electronic institutional and national registries and by contacting regional hospitals, patients, and their relatives.

Costs of treatment in the cardiac surgical ICU

Thirteen participating hospitals provided information on the estimates of daily expenditures of treatment in the cardiac surgery ICU (Supplementary Digital Material 2: Supplementary Table II). These costs refer to the average direct and indirect expenditures of treating adult cardiac surgery patients in the ICU as estimated by each hospital's administration. The daily costs of treatment with postcardiotomy extracorporeal membrane oxygenation were obtained from six hospitals and their mean estimate was added, as a separate analysis, to the mean estimate of costs of treatment in the cardiac surgical ICU when this salvage therapy was required.

Statistical analysis

Continuous variables were reported as the means and standard deviations as well as the medians and interquartile ranges (IQR). Categorical variables were reported as counts and percentages. Missing data were not replaced. The χ^2 test, the Fisher's Exact Tests and the linear-by-linear association test were used to analyze differences of categorical variables and the Mann-Whitney Test was used to compare continuous variables. The Kaplan-Meier method with the log-rank test was used to estimate the crude five-year mortality rates in the study cohorts. Multilevel mixed-effects linear regression, logistic regression and parametric survival methods were used to identify the independent predictors of the length of stay in the ICU, in-hospital mortality and five-year mortality, respectively, considering the cluster effect of the participating hospitals. Regression models included all risk factors as well as early adverse events listed in Supplementary Digital Material 3, Supplementary Table III. Risk estimates were reported as coefficients, odds ratios (ORs) and hazard ratios (HRs) with their 95% confidence intervals (CI). Calibration of the logistic regression model for identification of risk factors for in-hospital mortality was assessed by estimating the area under (AUC) the receiver operating characteristics curve (ROC), slope, expected/observed in-hospital mortality ratio and calibration-in-the-large. Comparative analysis of ROC curves was performed using the DeLong's Test. In-hospital mortality was significantly higher in patients who were treated only one day in the ICU. Since many of these patients might have had severe bleeding, acute heart failure or irreversible end-organ injury at admission to the ICU, they were excluded from further analyses. The length of ICU stay was dichotomized according to the median length of ICU stay of the entire series, *i.e.*, short ICU stay (≤5 days) and long ICU stay (>5 days). Multilevel mixed-effects logistic regression was performed to estimate the probability of being included in the short or long ICU stay cohorts considering the cluster effects of participating hospitals. All baseline and operative variables as well as early postoperative complications, but tracheostomy, listed in Supplementary Table III were included into the regression model considering the dichotomized (2-3 days *vs.* >5 days) ICU stay as the dependent variable. One-to-one propensity score matching was performed using a caliper width of 0.2 the standard deviation of the estimated logit (*i.e.*, 0.35). Standardized difference lower than 0.10 was considered as a non-significant imbalance of the covariates between the study cohorts. Two-sided P value less than 0.05 was considered statistically significant. Statistical analyses were performed with the SPSS (version 29.0, SPSS Inc., IBM, Chicago, Illinois, USA) and Stata (version 15.1, StataCorp LLC, College Station, TX, USA) statistical softwares.

Results

Patients

The ERTAAD dataset include data of 3735 consecutive TAAD patients (Supplementary Table I). Patients (N.=72) with missing data on the length of ICU stay and those who died intraoperatively (N.=125) were excluded from this analysis (Supplementary Digital Material 4: Supplementary Figure 1). Overall, 3538 fulfilled the inclusion criteria of this study. Their mean follow-up was 3.9±4.2 years (median, 2.5, IQR 6.2). Characteristics and operative variables of these patients as well as their early and late outcomes are summarized in Supplementary Table III. Independent baseline, operative and postoperative predictors of the length of stay in the ICU are listed in Supplementary Table III. Beside early postoperative adverse events, the magnitude of surgical procedure was associated with the length of treatment in the ICU (Supplementary Table III). Supplementary Digital Material 5, Supplementary Table IV summarizes the independent predictors of the length of ICU stay considering in the linear regression model only patients' baseline characteristics and operative variables.

Duration of ICU treatment and postoperative mortality

The mean length of ICU stay was 9.9±9.5 days (median 5.0 days, IQR 3.0-11.0). The number of patients according to the length of treatment in the ICU are summarized in Supplementary Digital Material 6, Supplementary Figure 2. Among these patients, the length of ICU stay was associated with crude in-hospital mortality (Mann-Whitney Test: P=<0.001, Linear-by-linear association test for classes of length of ICU stay, P<0.001). However, the in-hospital rate was markedly high (44.2%, 115/260) among patients who were treated only one day in the ICU (Supplementary Digital Material 7, Supplementary Figure 3). Supplementary Figure 3 demonstrates that crude in-hospital mortality rates did not vary markedly in patients with prolonged ICU stay and were close to the mean in-hospital mortality rate of the entire series. Indeed, when patients who were treated only one day in the ICU were excluded from the analysis, the mean length of ICU stay was 10.6±13.4 (median 6.0, IQR 3.0-12.0), and the length of ICU stay was not significantly associated with crude in-hospital mortality (Mann-Whitney Test: P=0.170; Linear-by-linear association test for classes of length of ICU stay, P=0.08). Supplementary Digital Material 8, Supplementary Figure 4 shows consonant results with high 5-year mortality rate among those patients treated only one day in the ICU. The crude 5-year mortality rates tended to increase in patients with a length of stay in the ICU >25 days (Supplementary Figure 4).

Adjusted analyses considered patients treated three days in the ICU as the reference group because they had the lowest crude in-hospital and five-year mortality rates (Supplementary Figure 3, Supplementary Figure 4). Independent predictors of in-hospital mortality are reported in Supplementary Table III. Analysis of the calibration of probabilities estimated by the multivariable multilevel mixed-effects logistic regression model in predicting in-hospital mortality showed and AUC of the model of 0.884 (95%CI 0.867-0.900), expected/observed mortality ratio of 0.993, calibration-in-the-large of 0.0013 and slope of 1.018 (Supplementary Digital Material 9, Supplementary Figure 5). When adjusted for these independent predictors, prolonged ICU stay was associated with significantly lower risk of in-hospital mortality (adjusted OR 0.971, 95%CI 0.959-0.982) (Supplementary Table III). The AUC of the regression model did not significantly improve after including the length of ICU stay (AUC 0.885, 95%CI 0.867-0.902, P=0.752). Patients treated in the ICU >13 days had lower adjusted risk of in-hospital mortality when the reference group were patients treated three days in the ICU (Figure 1).

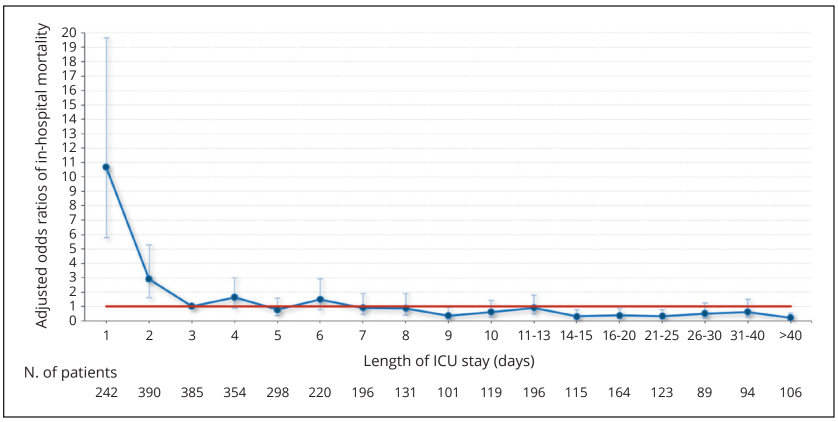

Figure 1.—Adjusted odds ratios of in-hospital mortality rates according to the length of stay in the ICU. The red line refers to an odds ratio of 1.0. Bars are 95% confidence intervals of the estimates (colors in the online version).

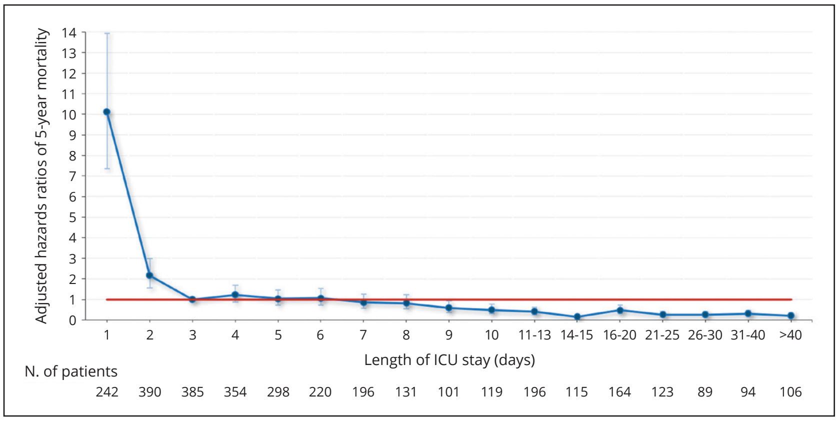

Figure 2.—Adjusted hazards ratios of 5-year mortality according to the length of stay in the ICU. The red line refers to a hazard ratio of 1.0. Bars are 95% confidence intervals of the estimates (colors in the online version).

The independent predictors of 5-year mortality are listed in Supplementary Table III. When adjusted for these independent predictors, prolonged ICU stay was associated with significantly lower risk of 5-year mortality (adjusted OR 0.970, 95%CI 0.962-0.977) (Supplementary Table III). When adjusted for these independent risk factors, patients treated in the ICU >8 days had significantly lower adjusted risk of 5-year mortality (Figure 2).

Prognostic impact of short and long icu stay in patients with ICU stay >1 day

We observed an excessive in-hospital mortality (44.2%) among patients who were treated only one day in the ICU. Likely many of these patients were transferred to the ICU in critical, intractable postoperative conditions. After excluding 260 patients who were treated only one day in the ICU, the outcomes of 3278 patients with a length of ICU stay >1 day were evaluated. The mean length of stay on this subset of patients was 10.6±13.4 days (median 6.0 days, IQR 9.0). This cohort of patients was dichotomized according to the median of the length of ICU stay, *i.e.*, short ICU stay (2-5 days) and long ICU stay (>5 days). Propensity score matching yielded 870 pairs of patients with comparable baseline and operative variables as well as early adverse events as demonstrated by standardized differences <0.1 in all covariates (Supplementary Digital Material 10, Supplementary Table V). Patients with prolonged ICU stay (>5 days) had significantly lower in-hospital mortality (8.9% *vs.* 17.4%, <0.001) and five-year mortality (28.2% *vs.* 20.7%, P=0.007,

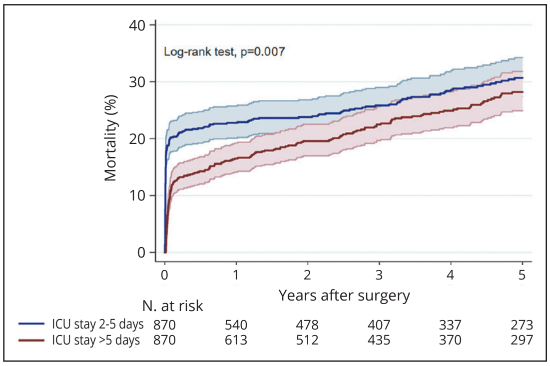

Figure 3.—Five-year mortality rates in propensity score matched pairs of patients with a short (2-5 days) and long (>5 days) stay in the ICU. Light blue and pink areas are 95% confidence intervals of the mortality risk estimates (colors in the online version).

Figure 3) compared to patients with short ICU-stay (2-5 days).

Daily and overall costs of ICU treatment

The mean value of daily expenditures for ICU treatment was 2404±888 € (median 2245 €, IQR 693 €). The estimated daily costs of postcardiotomy extracorporeal membrane oxygenation therapy were a mean value of 4008±2014 € (median 3964 €, IQR 1891 €). The overall costs of treatment in the cardiac surgery ICU considering the mean values gathered from the participating hospitals was a mean of 23862±31629 € (median 12020 €, IQR 19232 €) (Supplementary Table III). When the mean costs of postcardiotomy extracorporeal membrane oxygenation were also considered, the overall daily expenditures were a mean of 24086±32084 € (median 14420 €, IQR

19232). The overall costs of treatment in the cardiac surgery ICU considering the mean values gathered from the participating hospitals was a mean of 23732±40136 € (median 12020 €, IQR 21636) in patients who died during the index hospitalization and 23884±29913 € (median 14424 €, IQR 19232) in patients alive at discharge (adjusted for independent predictors of in-hospital mortality, P<0.001). When also the mean costs of postcardiotomy extracorporeal membrane oxygenation were considered, the overall expenditures were a mean of 24703±41377 € (median 12020 €, IQR 21636) in patients who died during the index hospitalization and 23979±30185 € (median 14424 €, IQR 19232) in patients alive at discharge (adjusted for independent predictors of in-hospital mortality, P<0.001). Prolonged ICU stay (>5 days) was associated with significantly higher costs compared to patients with short ICU-stay (2-5 days) (mean 8533±2635 €; median 9616 €, IQR 2404 *vs.* mean 30616±28690 €; median 21636 €, IQR 16828, P<0.001).

Discussion

The main results of the present study can be summarized as follows: 1) a significant number of patients who survived surgery for acute TAAD required prolonged ICU treatment; 2) when adjusted for multiple baseline, operative and postoperative covariates, prolonged ICU stay was associated with favorable in-hospital survival; 3) survival benefit of patients who required prolonged ICU treatment persisted up to five years after surgery; 4) extensive surgical repair and major postoperative neurological, renal and bleeding complications contributed to prolonged ICU stay; 5) the estimated expenditures of ICU treatment after surgery for acute TAAD was significant.

The prognostic impact of prolonged ICU treatment after surgery for acute TAAD has not been previously investigated. This issue has several implications in terms of resource allocation as well as of policy of intensive therapies for TAAD patients. Contrary to the present findings, previous studies demonstrated a negative prognostic impact of prolonged ICU treatment in cardiac surgery patients.[7] However, in the setting of emergency surgical repair of TAAD, clinicians are facing patients whose conditions are often critical at the onset of TAAD and may worsen after surgery. These conditions translate into a risk of mortality which is highest shortly after surgery (Figure 1 and Figure 2). In fact, mortality rates seem to decrease markedly in patients requiring three days of ICU treatment and, when adjusted for multiple variables, may further decrease in those patients with prolonged ICU stay. These findings should be considered in the light of a very high incidence of postoperative end-organ complications. Therefore, when pre- and postoperative complications are not deemed incurable, failure to rescue may be mostly related to the time and efforts spent to ameliorate these complications. In 1992, Silber *et al.*[8] observed that the adverse occurrence rate was associated primarily with patient characteristics, while failure to rescue was associated more with hospital characteristics and less influenced by severity of illness of patient at admission. In the setting of patients undergoing emergency surgery for acute TAAD, we expect that a policy of prolonging the time of care to ameliorate severe complications might have been a key factor in rescuing these patients.

This study showed that expenditures for ICU treatment of surgically treated TAAD patients are significant. The daily costs of ICU treatment as herein calculated were close to those estimated in Canada (2800 C$, *i.e.* about 1900 €) in patients treated between 2011 and 2016.[9] A pooled analysis estimated that the daily expenditures of ICU treatment in Belgium were 2160 €, without increased costs for cardiac surgery compared to other specialties.[10] In 2016, Gershengorn *et al.*[11] estimated daily costs of cardiac surgical ICU treatment ranging from 2060 US$ to 2325 US$ (*i.e.*, 1889 € to 2142 €), with the highest costs of 5166 US$ (4760 $) associated with the first day of ICU treatment. Takala *et al.*[12] estimated that, between 2015 and 2017, the daily costs of ICU treatment in Finland, Estonia and Switzerland were about 2100 €. However, we recognize that these valuations may largely underestimate the costs of ICU treatment in TAAD patients, because of their peculiar high risk of postoperative respiratory failure, acute kidney injury, severe bleeding, and neurological complications.

The length of treatment in the ICU depends on the current severity of patient's conditions and her/his comorbidities. We may expect that when ICU stay is improperly prolonged, it may lead to the development of other complications such as infections or neuropsychological derangements. However, the duration of treatment in the ICU is usually limited to the time strictly necessary to care for the critically ill patient. Indeed, the high costs of ICU therapies and the limited number of available ICU beds for the treatment of patients in need of cardiac surgery are critical factors considered in the decision-making process of whether discharge the patient to the sub-ICU, to the surgical or medicine ward, or even to peripheral hospitals. Consequently, when the patient has not yet achieved complete stability, early discharge from the ICU can be deleterious as acute worsening of organ functions may not be promptly recognized and treated. This may lead to an increased risk of failure to rescue from severe complications after surgery for TAAD.

Limitations of the study

This study has several limitations which should be considered when evaluating the present findings. The retrospective nature of the registry is the main limitation of this study. Second, we do not have data on readmissions to the cardiac surgical ICU, which might have contributed to a better understanding of the potential benefits of prolonged ICU stay in reducing the risk of major complications occurring the surgical ward. Third, the severity of some major adverse events such as stroke/global brain ischemia and heart failure were not graded in this registry, and most likely might have contributed to the increased mortality in patients with short ICU stay. Indeed, adjusted analysis does not allow a throughout analysis of the prognostic impact of these adverse events during a short stay in the ICU and on the increased risk of in-hospital mortality during the early postoperative days. Considering these limitations, we may expect that many patients with prolonged ICU stay, despite having had a higher incidence of adverse events (Supplementary Table V), were not in critical conditions and this has supported the decision of their prolonged treatment in the cardiac surgical ICU. Fourth, there is a large inter-institutional variability in terms of early and late mortality rates (Supplementary Table I), which to some extent may reflect the case-mix of these hospitals. However, we may notice that a few hospitals adopted a strategy of prolonged ICU treatment which was associated with favorable outcomes (Supplementary Table I). The cluster effect of participating hospitals and the related inter-institutional differences in the referral pathway and perioperative care have been considered using multilevel mixed-effects regression analyses. Finally, we do not have data on ICU mortality. Data on this outcome was not gathered because we expected that some patients with incurable complications were transferred to surgical ward after withdrawing treatment.

Conclusions

In conclusion, prolonged ICU stay was common after surgery for acute TAAD and requires significant resources. Still, when adjusted for multiple baseline and operative variables as well as adverse postoperative events and the cluster effect of hospitals, it can be associated with favorable survival up to five years after surgery. These findings should be viewed in the light of unfavorable outcome of patients who had a short ICU stay because of a combination of severe preoperative and postoperative conditions typical of TAAD patients. Despite these limitations, a thoughtful decision-making process of prolonging treatment in the ICU can be associated with a good prognosis in many critically ill TAAD patients. Data on the functional recovery of these patients is vital to evaluate the individual and societal benefits of allocating significant resources for intensive care of TAAD patients with severe complications.

What is known

- The outcomes after prolonged treatment in the ICU after surgery for Stanford TAAD have not been previously investigated.

What is new

- Prolonged ICU stay was common after surgery for acute TAAD and was associated with significant costs.

- Patients requiring prolonged ICU stay had favorable survival up to five years after surgery.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Fausto Biancari, Amelié Hérve and Andrea Perrotti: conceptualization, data curation, formal analysis, methodology, writing – original draft, writing – review and editing; Timo Mäkikallio, Tatu Juvonen, and Mikko Jormalainen: conceptualization, funding acquisition, writing – review and editing; Sven Peterss, Caroline Radner, Joscha Buech, Matteo Pettinari, Javier Rodriguez Lega, Angel G. Pinto, Antonio Fiore, Francesco Onorati, Alessandra Francica, Till Demal, Lenard Conradi, Jan Rocek, Petr Kacer, Giuseppe Gatti, Igor Vendramin, Mauro Rinaldi, Luisa Ferrante, Robert Pruna-Guillen, Eduard Quintana, Dario Di Perna, Giovanni Mariscalco, Mikko Jormalainen, Mark Field, Amer Harky, Angelo M. Dell'Aquila: conceptualization, data curation, writing – review and editing. All authors read and approved the final version of the manuscript. All authors read and approved the final version of the manuscript.

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Supplementary data
For supplementary materials, please see the HTML version of this article at www.minervamedica.it