CRITICAL ROUNDS

MICRO LABS LIMITED

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Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring "CRITICONNECT" containing latest information in the field of Critical care medicine.

Inside This Issue

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Best Regards,
Medical Team, Micro Labs Ltd

CRITICAL ROUNDS

Argatroban versus heparin in patients without heparin-induced thrombocytopenia during venovenous extracorporeal membrane oxygenation: a propensity-score matched study

Introduction

The use of extracorporeal membrane oxygenation (ECMO) has been steadily increasing, particularly during the 2009–2010 H1N1 influenza-A pandemic and the recent COVID- 19 pandemic. Bleeding and thrombosis as side effects of ECMO therapy are still very common and have a critical impact on outcome. Due to the activation of the coagulation cascade by nonendothelial artificial surfaces, unfractionated heparin (UFH) is the anticoagulation regime currently recommended by the Extracorporeal Life Support Organization (ELSO). However, alternative anticoagulation strategies are being investigated, and direct thrombin inhibitors (DTI) have been proposed to have potential advantages. When using Argatroban as anticoagulant in critically ill patients, specific attention has to be paid to the initial requirement of a much lower dosage to impede bleeding events. A distinct disadvantage of UFH is the risk of type II heparin induced thrombocytopenia (HIT), which has been reported in up to 4% of patients on ECMO support. Knowledge about the pros and cons of the different anticoagulation substances in clinical ECMO practice is still scarce, and comparative studies are lacking.

Aim: To investigate if Argatroban is non-inferior to UFH with respect to the occurrence of thrombosis and bleeding in patients without HIT during vvECMO support.

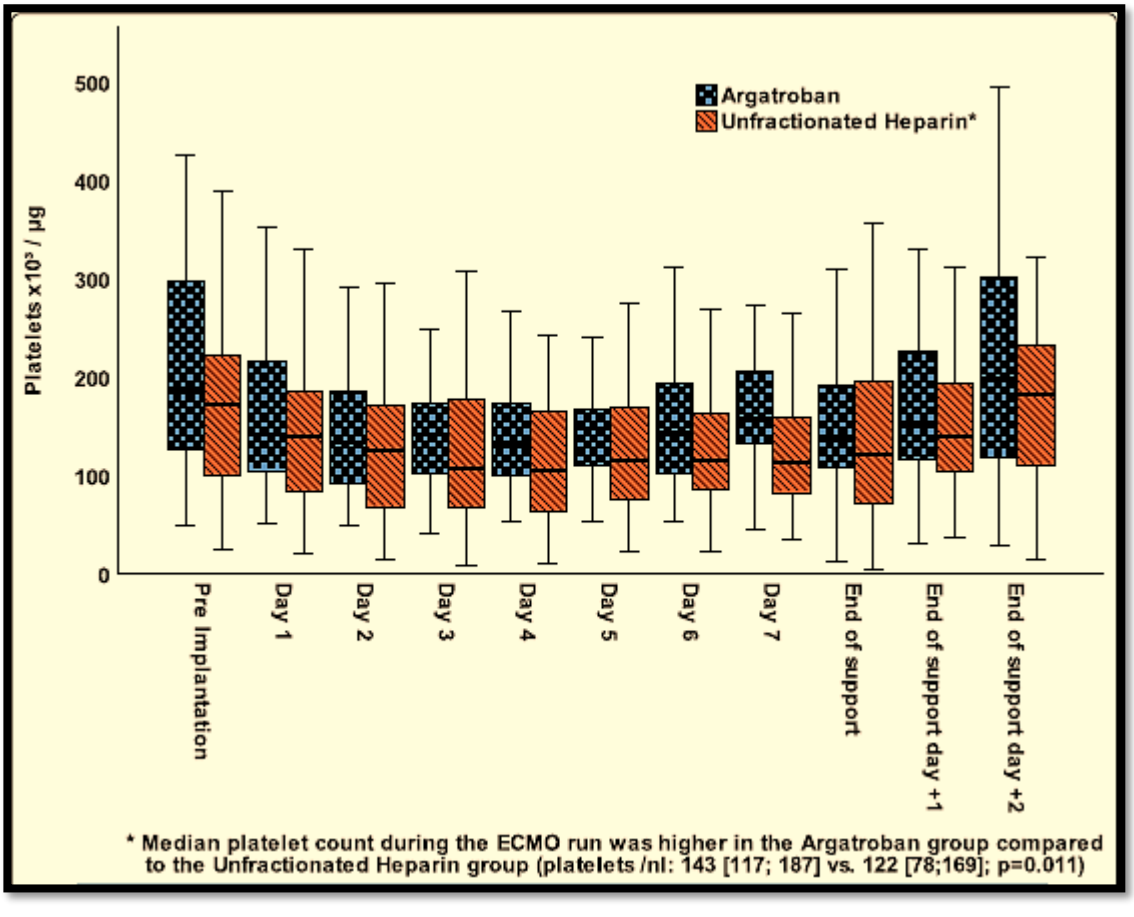
Methods: A propensity-score matched observational non-inferiority study of consecutive patients without heparin-induced-thrombocytopenia (HIT) on vvECMO, treated between January 2006 and March 2019 in the medical intensive care unit at the University Hospital Regensburg. Anticoagulation was realized with UFH until August 2017 and with Argatroban from September 2017 onwards. Target activated partial thromboplastin time was 50 +/- 5 seconds in both groups.

Primary composite endpoint: Major thrombosis and/or major bleeding.

Secondary endpoint: Technical complications such as oxygenator defects or pump head thrombosis, the time-course of platelets, and the cost of anticoagulation were also assessed.

Results: Out of 465 patients receiving UFH, 78 were matched to 39 patients receiving Argatroban. The primary endpoint occurred in 79% of patients in the Argatroban group and in 83% in the UFH group (non-inferiority for Argatroban, $p = 0.026$).

Box plot of the course of platelets throughout ECMO support according to anticoagulation. Data are expressed as median, minimum, maximum, 25. Percentile, and 75. Percentile



Comparison between the Argatroban and the unfractionated heparin group: secondary endpoints: thrombosis, bleeding, transfusion, and cerebral pathologies

Variables	Argatroban n = 39	UFH n = 78	*p* value
Major thrombosis	11 (28)	13 (17)	0.145
Pulmonary embolism on ECMO	2 (5)	3 (4)	0.747
ECMO days per oxygenator	9 (6; 12)	8 (6; 10)	0.210
Major bleeding	27 (69)	63 (81)	0.163
RBC transfusion per day on ECMO	0.3 (0; 0.5)	0.3 (0; 0.7)	0.287
FFP transfusion per day on ECMO	0.0 (0; 0)	0.0 (0; 0)	0.063
Platelet transfusion/day on ECMO	0.0 (0; 0)	0.0 (0; 0.1)	**0.044**
Cerebral hemorrhage	2 (5)	8 (10)[a]	0.584
Successful discharge from hospital	30 (77)	47 (60)	0.073
SOFA score at the end of ECMO support	6.0 (4; 8)	5.0 (3; 7)	0.058

The occurrence of technical complications was equally distributed (Argatroban 49% vs. UFH 42%, $p = 0.511$). The number of platelets was similar in both groups before ECMO therapy but lower in the UFH group after end of ECMO support (median [IQR]: 141 [104;198]/nl vs. 107 [54;171]/nl, $p = 0.010$).

Conclusion: Patients without HIT on vvECMO, Argatroban was non-inferior to UFH regarding bleeding and thrombosis. The occurrence of technical complications was similarly distributed. Argatroban may have less impact on platelet decrease during ECMO, but this finding needs further evaluation. Direct drug costs were higher for Argatroban but comparable to UFH after accounting for HIT-testing and transfusions.

Source: Fisser et al. Argatroban versus heparin in patients without heparin-induced thrombocytopenia during venovenous extracorporeal membrane oxygenation: a propensity-score matched study Crit Care (2021) 25:160.

CRITICAL ROUNDS

Cardiac biomarkers in acute respiratory distress syndrome: a systematic review and meta-analysis

Introduction

Acute respiratory distress syndrome (ARDS) is a leading cause of morbidity and mortality in the intensive care unit (ICU). A heterogeneous clinical condition, its definition relies on the exclusion of acute respiratory failure secondary to left heart failure or fluid overload. Prognostic factors identified for this condition include age, ethnicity, comorbidities, illness severity scores, PaO2/FiO2 ratios and ventilatory parameters. Patients with ARDS and high baseline risk of mortality may respond differently to treatment. Early identification of these patients using a biomarker may be useful in guiding clinical management. Biomarkers of cardiac stretch such as brain natriuretic peptide (BNP) and N-terminal-probrain-natriuretic-peptide (NT-proBNP) are well established in the diagnosis and prognosis of heart failure. Similarly, biomarkers of cardiac injury, such as Troponin-T and Troponin-I, are valuable in the diagnosis and prognostication of myocardial infarction. These biomarkers also have prognostic value in pulmonary diseases such as pneumonia and chronic obstructive pulmonary disease.

Aim: To examine the association between biomarkers of cardiac stretch or cardiac injury and short-term mortality in patients with ARDS.

Methods: A systematic review of MEDLINE, EMBASE, Web of Science and CENTRAL databases was performed. Studies of adult intensive care patients with ARDS that reported the risk of death in relation to a measured biomarker of cardiac dysfunction were included.

Primary outcome: Mortality up to 60 days.

Results: Twenty-two studies were included in the systematic review and 18 in the meta analysis. Biomarkers of cardiac stretch included NT-ProBNP (nine studies) and BNP (six studies). Biomarkers of cardiac injury included Troponin-T (two studies), Troponin-I (one study) and High-Sensitivity-Troponin-I (three studies).

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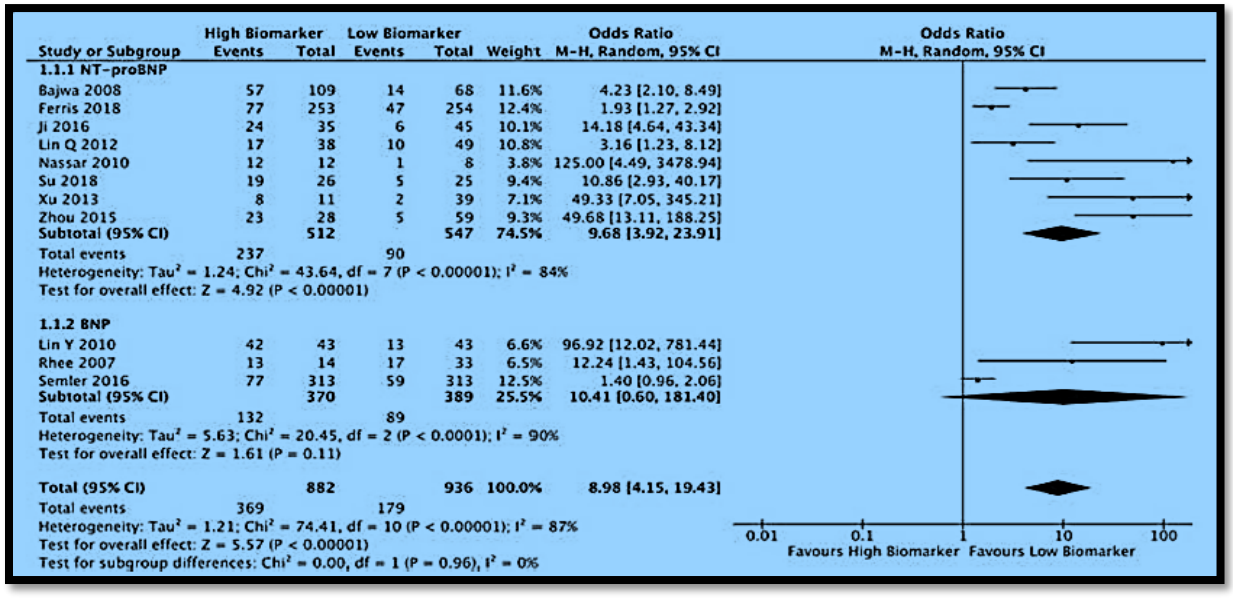
Biomarkers of cardiac stretch and mortality forest plot



Biomarkers of cardiac injury and mortality forest plot

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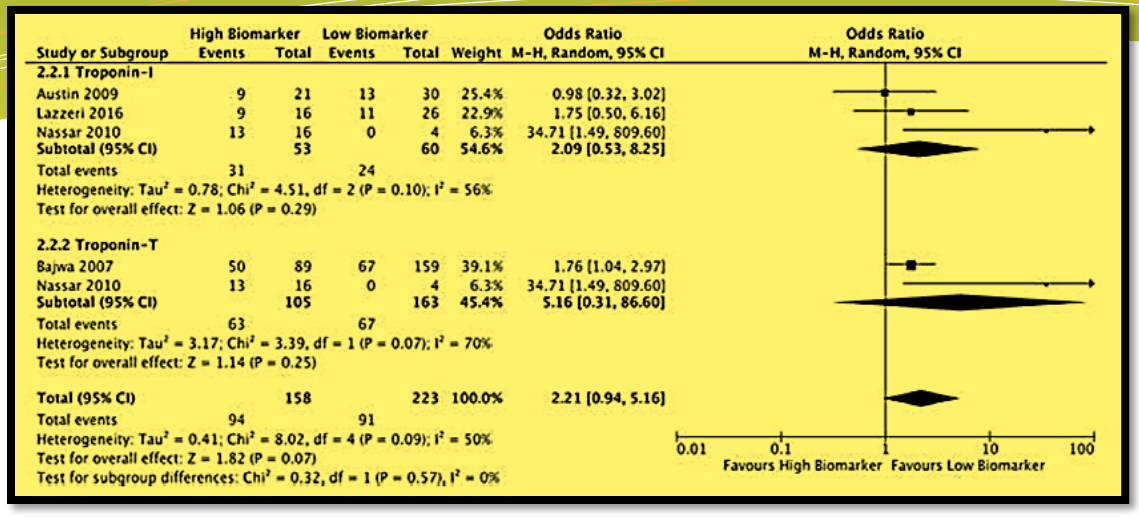


Three studies assessed multiple cardiac biomarkers. High levels of NT-proBNP and BNP were associated with a higher risk of death up to 60 days (unadjusted OR 8.98; CI 4.15-19.43; p<0.00001). This association persisted after adjustment for age and illness severity. Biomarkers of cardiac injury were also associated with higher mortality, but this association was not statistically significant (unadjusted OR 2.21; CI 0.94-5.16; p= 0.07).

Conclusion:

High levels of brain natriuretic peptides, indicating cardiac stretch, are associated with a higher risk of death in patients with ARDS independently of other commonly used prognostic indicators. Further studies are required to determine if a similar relationship exists between cardiac troponins and mortality in ARDS. Biomarkers of cardiac stretch are associated with increased mortality in ARDS.

Source: Jayasimhan et al. Cardiac biomarkers in acute respiratory distress syndrome: a systematic review and Meta-analysis Journal of Intensive Care (2021) 9:36

CRITICAL ROUNDS

Temporal patterns of organ dysfunction after severe trauma

Background

Organ dysfunction (OD) may be a major risk to critically injured patients surviving through the resuscitation phase. It creates a big clinical challenge within the medical care unit (ICU)-treated trauma patient and is related to prolonged length of stay (LOS), adverse outcomes, and demanding resource utilisation. With more patients surviving through the first trauma phase, thanks to advances in trauma care systems, OD becomes an increasing determinant of outcome. The trajectories of OD, in terms of severity and composite temporal patterns and determination , are complex and diverse. Monitoring and treating in reference to temporal patterns of composite physiological states is inherent to ICU strategy. Each patient could also be unique in their response. Understanding these patterns may help in timing of treatment strategies, pre-emptive identification of impending clinical decline, and to spot cohorts that within the future may require precision treatment approaches identified with predictive enrichment strategies. Despite these discernible prerequisites and notable pursuits, ICU and trauma research need to date been

more focused on temporally static approaches to pattern recognition. As such, important steps towards identifying composite phenotypes of disease within the ICU are taken for ICU-related diseases like ARDS and sepsis, but rely predominantly on early presentation data and patterns, and take less under consideration information content found within the temporal evolution of disease. Thus, there's a transparent got to align pattern recognition with clinical temporal reasoning and human-interpretable models, albeit this necessitates complex methods of time-series analysis and pattern recognition. Group-based trajectory modelling (GBTM), as developed and described by Nagin and Odgers, generally fit polynomials, over time for a gaggle of trajectories, using maximum likelihood estimation to a predefined number of categories. it's a specialised application of the finite mixture model, a probabilistic modelling to spot subpopulations. The optimal number of trajectories may to some extent be objectified using Akaike or Bayesian information criterion (AIC or BIC), with BIC driving more parsimonious solutions. it's been used for variety of real-world clinical data analyses to spot temporal trajectories and affords a compelling method to scale back high-dimensional temporal data to a finite number of comparable “type” trajectories.

Aim: To analyse the temporal patterns of OD in ICU-treated critically injured patients.

Methods: A group-based trajectory modelling to identify temporal trajectories of OD after trauma. Modelling was based on the joint development of all six subdomains comprising the sequential organ failure assessment

score measured daily during the first two weeks post trauma. Further, the time for trajectories to stabilise and transition to final group assignments were evaluated.

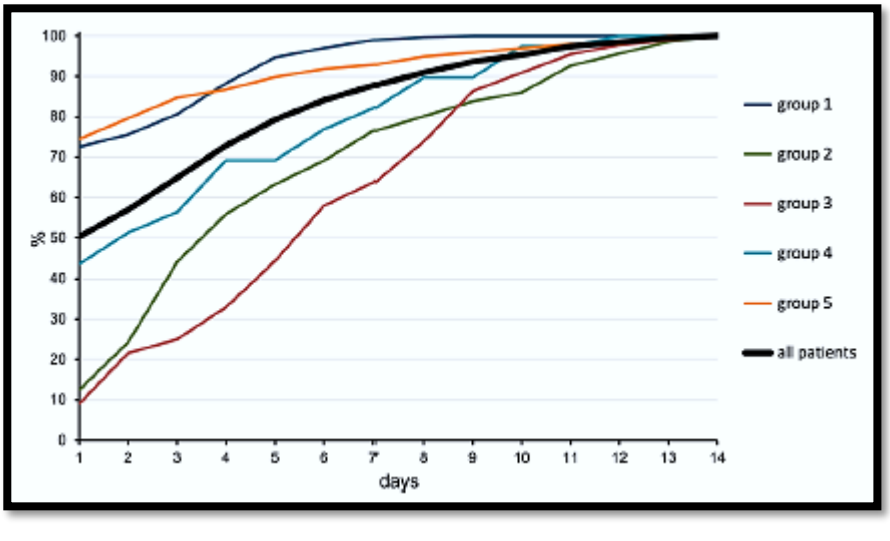
Results: Six-hundred and sixty patients were included in the final model. Median age was 40 years, and median ISS was 26 (IQR 17–38). We identified five distinct trajectories of OD.

Outcomes

Factor	All patients	Group 1	Group 2	Group 3	Group 4	Group 5
n	660	300	135	87	40	98
ICU LOS	3.4 (1.9–8.0)	2.1 (1.5–2.9)	5.7 (4.6–7.7)	13 (9.9–16)	18 (7.3–27)	4.1 (1.9–16)
Hospital LOS	16 (9.4–30)	11 (6.9–17)	19 (13–26)	29 (21–42)	41 (16–72)	26 (3.9–46)
ICU mortality	47 (7.1%)	1 (0.3%)	1 (0.7%)	2 (2.3%)	10 (25%)	33 (34%)
28-day mortality	63 (9.5%)	8 (2.7%)	4 (3.0%)	4 (4.6%)	12 (30%)	35 (36%)
Time to death	4.3 (2.5–10)	6.6 (3.6–11)	7.6 (3.3–11)	12 (9.9–15)	7.4 (2.3–14)	3.5 (2.4–4.8)
1-year mortality	80 (12%)	13 (4.3%)	7 (5.2%)	6 (6.9%)	14 (35%)	40 (41%)

Group 1, mild OD (n = 300), median ISS of 20 (IQR 14–27), had an early resolution of OD and a low mortality. Group 2, moderate OD (n = 135), and group 3, severe OD (n = 87), were fairly similar in admission characteristics and initial OD but differed in subsequent OD trajectories, the latter experiencing an extended course and higher mortality. In group 3, 56% of the patients developed sepsis as compared with 19% in group 2. Group 4, extreme OD (n = 40), received most blood transfusions, had the highest proportion of shock at admission and a median ISS of 41 (IQR 29–50). They experienced significant and sustained OD affecting all organ systems and a 28-day mortality of 30%. Group 5, traumatic brain injury with OD (n = 98), had the highest mortality of 35% and the shortest time to death for non-survivors, median 3.5 (IQR 2.4–4.8) days. Groups 1 and 5 reached their final group assignment early, > 80% of the patients within 48 h. In contrast, groups 2 and 3 had a prolonged time to final group assignment.

Trajectory stabilisation over time



Conclusions:

Five distinct trajectories of OD after severe trauma during the first two weeks posttrauma were observed. These findings underline the heterogeneous course after trauma and describe some potentially important clinical insights that are suggested by the groupings and temporal trajectories.

Source: Eriksson et al. Temporal patterns of organ dysfunction after severe trauma. Crit Care (2021) 25:165