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Low-Molecular-Weight Heparin Compared to Unfractionated Heparin in Critically Ill COVID-19 Patients

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Short Title: Low-Molecular-Weight vs Unfractionated Heparin in COVID-19 Patients

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This study was presented as a virtual poster at the 2021 Eastern Vascular Society conference, Charleston, South Carolina, September 23-26, 2021.

Article Highlights

Type of Research: Single-center retrospective cohort study

Key Findings: Of 218 patients, 135 received Low-Molecular-Weight Heparin and 83 received unfractionated Heparin. Among intubated critically ill COVID-19 ICU patients, therapeutic AC, with either LMWH or UFH, conveyed no survival benefit over prophylactic AC. AC with LMWH was associated with higher cumulative survival compared to AC with UFH.

Table of Contents Summary: In this retrospective single-center cohort study of 218 critically ill intubated COVID-19 patients, therapeutic AC conveyed no survival benefit over prophylactic AC. AC with LMWH was associated with higher cumulative survival compared to AC with UFH.

Abstract

Background. Thrombosis in COVID-19 worsens mortality. In our study we sought to investigate how the dose and type of anticoagulation (AC) can influence patient outcomes.

Methods. This is a single-center retrospective analysis of critically ill intubated COVID-19 patients, comparing low molecular weight heparin (LMWH) and unfractionated heparin (UFH) at therapeutic and prophylactic doses. Of 218 patients, 135 received LMWH (70 prophylactic, 65 therapeutic) and 83 UFH (11 prophylactic, 72 therapeutic). The primary outcome was mortality. Secondary outcomes were thromboembolic complications confirmed on imaging and major bleeding complications. Cox proportional-hazards regression models were utilized to determine
whether the type and dose of AC were independent predictors of survival. We performed
Kaplan-Meier survival analysis to compare the cumulative survivals.

Results.
Overall, therapeutic AC, with either LMWH (65% versus 79%, P-value 0.09) or UFH (32%
versus 46%, P-value 0.73), conveyed no survival benefit over prophylactic AC. UFH was
associated with a higher mortality rate than LMWH (66% versus 28%, P-value 0.001), which
was also evident in the multivariable analysis (LMWH versus UFH mortality HR: 0.47, P-value
0.001) and in the Kaplan-Meier survival analysis. Thrombotic and bleeding complications did
not depend on the AC type (prophylactic LMWH vs. UFH: thrombosis P-value 0.49, bleeding P-
value 0.075, therapeutic LMWH vs. UFH: thrombosis P-value 0.5, bleeding P-value 0.17). When
comparing prophylactic to therapeutic AC, the rate of both thrombotic and bleeding
complications was higher with the use of LMWH compared with UFH. Additionally, transfusion
requirements were significantly higher with both therapeutic LMWH and UFH.

Conclusions. Among intubated critically ill COVID-19 ICU patients, therapeutic AC, with either
LMWH or UFH, conveyed no survival benefit over prophylactic AC. AC with LMWH was
associated with higher cumulative survival compared to AC with UFH.

Keywords: COVID-19, SARS-CoV-2, Low-Molecular-Weight Heparin (LMWH),
Unfractionated Heparin (UFH), Thromboprophylaxis, Anticoagulation (AC)

Introduction
The COVID-19 pandemic has led to a global health crisis with more than 471 million cases and
6 million deaths [1]. The high mortality associated with COVID-19 is partially related to
microvascular [2], and macrovascular thromboembolic complications [3, 4, 5], attributed to
SARS-CoV-2 induced thrombo-inflammation [6] and hypercoagulability [7]. The International Society on Thrombosis and Hemostasis recommended using prophylactic-doses of LMWH for all hospitalized COVID-19 patients unless they have active bleeding or low platelet count (< 25 x 10^9/L) [8], while further guidelines also stated to consider a 50% increase in the dose of thromboprophylaxis in obese patients [9]. Recent randomized controlled clinical trials have demonstrated increased survival to discharge in non-critically COVID-19 patients while no benefit was seen in critically ill patients [11,12]. In this study, we sought to identify whether the different types of AC; LMWH versus UFH, and AC level, prophylactic versus therapeutic, can have an impact on patient mortality, and the development of thrombotic and bleeding complications. We also evaluated the correlation between the type of AC and COVID-19 inflammatory markers such as CRP and IL-6 to demonstrate any potential anti-inflammatory properties of LMWH and UFH in critically ill patients affected by the SARS-CoV2 [10].

Methods

Ethics Statement

This study was a retrospective chart review of a COVID-19 patient database. Stony Brook University Committee on Research in Human Subjects approved the study protocol and supervised all study procedures according to state and federal regulations, with a waiver of informed consent.

Target Population and Data Sources

We identified all critically ill intubated COVID-19 patients admitted to Stony Brook University Hospital between February 7, 2020, and May 17, 2020. The diagnosis of COVID-19 was based on positive RT-PCR test for SARS-CoV-2. Aside from the difference in the AC type and dose,
the patients were treated in the same manner for all aspects of COVID-19 disease. We selected
the study population based on the following criteria: age $\geq$ 18 years old, RT-PCR proven
COVID-19, initiation, and administration of chemical AC regimen for at least 24 hours, and
respiratory failure requiring endotracheal intubation. Patients were excluded from the study if
AC was never started, or the administered AC was other than LMWH or UFH. As many people
were intubated soon after their presentation to the emergency department, we elected to exclude
those who were receiving oral AC prior to hospital admission to avoid any bias in our analysis
which targeted to compare the effectiveness of LMWH versus UFH.

**Electronic Medical Record (EMR) Review**

We reviewed each EMR and collected the following data: demographics (age, gender, BMI),
dates of admission, intubation, comorbidities (HTN, COPD, CHF, DM, CKD), laboratory data
(D-dimer, CRP, creatinine, IL-6), SOFA score which was calculated based on lab values
obtained at the time of intubation and for 24 hours subsequently, thromboembolic complications,
both venous (DVT, PE) and arterial (MI, stroke, peripheral thrombosis), clinically significant
bleeding defined as: upper or lower gastrointestinal bleeding requiring transfusion of at least two
units of red blood cells, hemoglobin < 7 mg/dL, intracranial bleeding, other major bleeding
requiring transfusion, including massive hemoptyisis, hematuria, retroperitoneal hematoma,
intraperitoneal or intrathoracic bleeding, heparin-induced thrombocytopenia (HIT) and mortality.
An overall of 30 CT angiography scans and 20 Venous Duplex ultrasound scans were performed
in the whole cohort following clinical suspicion for VTE. For all patients, 5-month follow-up
data were available. All patients were included in the Kaplan-Meier analysis.

**AC protocol**
All patients admitted to Stony Brook University Hospital were placed at least on thromboprophylaxis regimen on admission, unless medically contraindicated. Our institution implemented an aggressive anticoagulation protocol, which included dose escalation based on daily measured D-dimer levels. Patients with D-dimer < 1,000 ng/mL received enoxaparin 40 mg daily, those with D-dimer ≥ 1,000 ng/mL but < 3000 ng/mL received enoxaparin 40 mg twice a day. Finally, those with D-dimer ≥ 3,000 ng/mL received therapeutic anticoagulation with enoxaparin 1 mg/kg twice a day or intravenous heparin drip at a starting rate of 18 units/kg/hr to achieve a goal PTT of 60 to 90. Therapeutic AC was also initiated whenever it was medically warranted, such as atrial fibrillation or suspected and confirmed venous thromboembolic disease (DVT, PE). Because of the absence of patient randomization, the type of AC was based on physicians’ preference and was characterized by wide heterogeneity as the patients were admitted in five different intensive care units that were managed by both medicine and surgery intensivists. When these patients were becoming critically ill, our institution was in the rapidly escalating pandemic curve. Although UFH was used more commonly in patients with known CKD or new AKI, LMWH was also used in patients despite creatinine elevation.

Data Analysis

Statistics

Statistical analyses were performed using SPSS 21.0 software (SPSS Inc, Chicago, Ill) and in-house developed coding in MATLAB. The significance level for all tests was 0.05. All reported P-values were calculated two-sided. The primary endpoint was mortality. Secondary endpoints were the development of thromboembolic and bleeding complications. Data were reported as group means and the two-tailed Student's T-statistic for several labs (D-dimer, CRP, creatinine, IL-6). We used chi-square test to compare categorical variables. Two-sample T-test or Mann-
Whitney U test were used for continuous variables as indicated based on normal distribution versus skewness of factors. Non-parametric Mann-Whitney U test analysis was performed to compare the means of maximum D-dimer, CRP, creatinine, and IL-6. Survival and its association with measured factors were evaluated using Kaplan-Meier models. Log-rank test was used to compare survival between groups. To determine whether the type and the level of AC were independent predictors of survival, we used Cox proportional-hazards regression models. Based on the univariable analysis we determined significant factors to be involved in the multivariable Cox regression model. These factors included age, gender, type of AC (UFH vs LMWH), level of AC (prophylactic vs therapeutic), SOFA score, steroid use. Entry-level for multivariable analysis was P-value <0.1. This model provided hazard ratios to estimate which parameters are independent predictors of survival. There was no missing data regarding survival measures.

Results

Study Population

Our study included 240 intubated patients Stony Brook University Hospital ICUs between February 7, 2020, and May 17, 2020. Twenty-two patients were excluded after implementation of the exclusion criteria, leaving 218 patients for analysis. We found 135 patients that received LMWH and 83 UFH. There was no significant difference in mean ages (P-value 0.7), BMI (P-value 0.7), and gender (P-value 0.062) between the LMWH and UFH groups. This cohort was divided based on therapeutic AC (65 on LMWH and 72 on UFH) and prophylactic AC dosing (once or twice daily thromboprophylaxis with 70 on LMWH and 11 on UFH) (Figure 1). There was no significant difference in the SOFA scores, calculated on the day of intubation, between
LWMH and UFH (P-value 0.5) in those who received therapeutic AC. However, there was a statistically significant difference in the prophylactic dose groups, with the SOFA score being slightly higher in those who received LMWH (P-value 0.04) (Table 1).

**Primary Outcomes**

**Mortality**

In the univariable survival analysis, sex (P-value 0.61), BMI (P-value 0.699), HTN (P-value 0.441), DM (P-value 0.583), CKD stage 3a-5 (P-value 0.153), CHF (P-value 0.253), COPD (P-value 0.284), steroid use (P-value 0.053) were not predictors of outcome. On the other hand, age above 70 years old (P-value 0.001), SOFA score above seven (P-value 0.002) and use of UFH instead of LMWH AC (P-value <0.0001) proved to be predictors of mortality. Multivariable analysis showed that patients who received UFH had higher mortality compared to patients who received LMWH, and this finding was independent of age, sex, or SOFA score (mortality LMWH vs UFH hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.30-0.74; P-value 0.001). Furthermore, male sex (HR, 1.68; 95% CI, 1.01-2.78; P-value 0.044), and age over 70 years old (HR, 2.15; 95% CI, 1.36-3.39; P-value <0.001) were also predictors of higher mortality. By contrast, SOFA score greater than seven (HR, 1.33; 95% CI, 0.86-2.06; P-value 0.188) and steroid use (HR, 1.50; 95% CI, 0.69-3.3; P-value 0.303) did not reach statistical significance in the multivariable analysis (Table 2).

We performed a subgroup analysis for creatinine level less than 1.3 measured at the initiation of the therapeutic dose of AC between those who received LMWH and UFH, to account for the potential selection bias, as UFH is more commonly used in patients with decreased renal function compared to using LMWH. Similarly, to the general cohort, mortality once more was
significantly lower in the LMWH group when compared to the UFH group (32.7% versus 64%, P-value 0.002).

In Kaplan-Meier survival analysis, patients who received LMWH had higher cumulative survival than patients who received UFH in both prophylactic and therapeutic groups (P-value 0.001) (Figure 2). Cumulative survival difference between prophylactic LMWH and therapeutic LMWH was not statistically significant (P-value 0.09). Similarly, the cumulative survival difference between prophylactic UFH and therapeutic UFH did not reach statistical significance (P-value 0.73) (Figure 2).

In our patient population, the most frequent cause of death was multisystem organ failure (MSOF) (75/93 patients, 31/38 in LMWH group, and 44/55 in UFH group), primarily driven by hypoxic respiratory failure. Other less common causes of death were myocardial infarction, lethal arrhythmias, and massive pulmonary embolism.

Secondary outcomes

Thromboembolic and bleeding events

There was no significant difference in thrombotic complications, both venous (DVT, PE) and arterial (MI, stroke, peripheral thrombosis) and bleeding complications (upper and lower GI bleed, hemothorax, mediastinal and tracheostomy site bleeding) when comparing LMWH and UFH in the therapeutic groups (LMWH vs UFH: thrombosis P-value 0.5, bleeding P-value 0.17). We observed similar results when we compared LMWH and UFH in the prophylactic groups (LMWH vs UFH: thrombosis P-value 0.49, bleeding P-value 0.075). However, we found that the transfusion requirements were significantly higher in those who received therapeutic LMWH and UFH (P-value 0.001). Notably, there was no difference in the prophylactic LMWH versus prophylactic UFH groups (P-value 0.17) (Table 3). For the VTE diagnosis a total of 30
CT angiography scans and 20 Venous Duplex ultrasound scans were performed following clinical suspicion for PE and DVT, respectively.

To establish the safety profile of the administration of therapeutic AC in the management of severe COVID-19, we further compared prophylactic versus therapeutic AC for the rates of thrombotic and bleeding complications. We found that the rate of thrombotic complications was higher with the use of therapeutic compared to prophylactic LMWH (LMWH *P*-value 0.051) and the same between prophylactic and therapeutic doses of UFH (UFH *P*-value 0.45). Bleeding complications were higher in the therapeutic LMWH than prophylactic LMWH (*P*-value 0.002) but not different between prophylactic and therapeutic UFH groups (*P*-value 0.35). The rate of blood transfusions was higher with therapeutic than prophylactic AC for both LMWH and UFH (LMWH *P*-value 0.002, UFH *P*-value 0.0008) (Table 3).

**Laboratory results: CRP and D-dimer levels**

There was no significant difference in the maximum CRP levels between the therapeutic and prophylactic groups among those who received LMWH and UFH (Table 1). Notably, the CRP peak in both groups occurred early in the hospital course and reduced following AC treatment, both in those who received LMWH and UFH. (Figure 3).

Prophylactic AC with LMWH was associated with a significantly lower max IL-6 level in COVID-19 intubated patients when compared with the UFH group (*P*-value 0.003), although our data were limited (n=6). However, there was no statistically significant difference in the maximum IL-6 level between LMWH and UFH in those who received therapeutic AC (n=35) (*P*-value 0.6) (Table 1).

Maximum D-dimer levels were not statistically different between therapeutic and prophylactic groups among patients who received LMWH and UFH (Table 1). The D-dimer peak occurred
early in the ICU course matching the time of AC initiation, and following the same trend as CRP, gradually down-trended over the hospital course (Figure 3).

Discussion

Our study found that in critically ill intubated patients hospitalized with COVID-19, therapeutic AC did not affect the cumulative survival compared to prophylactic AC, with either LMWH or UFH. Our findings are in line with the most lately published National Institution of Health guidelines, according to which therapeutic doses of heparin has no significant benefit in patients with COVID-19 admitted to the ICU, unless VTE is confirmed [13]. We analyzed patients that suffered from COVID-19 during the first wave of the pandemic, when no official guidelines for AC in COVID-19 existed. Our decision to implement an aggressive AC protocol, similar to a protocol proposed by the European Society of Cardiology [15] was based on our observation that severe arterial and venous thromboembolic events emerged despite the use of routine thromboprophylaxis. Although the escalation of AC to high intensity thromboprophylaxis and furthermore to therapeutic AC in our cohort of patients was associated with significantly improved organ function and overall survival [14], and that this practice might be able to balance the negative effects of obesity on the overall patient mortality [16], the most updated NIH guidelines recommend against this practice and advice over de-escalation of AC once patients get admitted to the ICU [13]. The cornerstone of these recommendations is based on two randomized controlled clinical trials by the REMAP-CAP/ACTIV-4a/ATTACC investigators who showed that although the strategy to administer therapeutic AC increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with the administration of prophylactic AC in non-critically ill
patients [11], this benefit disappeared in critically ill patients who received ICU level of care [12]. We also support the hypothesis that has been made by the clinical trial investigators that the initiation of therapeutic AC after severe COVID-19 has developed may be too late to alter the consequences of established disease processes [12].

We also found that in critically ill intubated patients hospitalized with COVID-19, UFH was associated with higher mortality rate compared to those who received LMWH, regardless of the AC level, prophylactic or therapeutic. LMWH has been the mainstay AC regimen in most studies, as it was shown early in the COVID-19 pandemic to be associated with better prognosis, especially in severe COVID-19 patients with sepsis induced coagulopathy score (SIC) score ≥4 or D-dimer >6-fold of upper limit of normal [17]. Our observation regarding the superiority of LMWH agrees with the findings from a large intention to treat trial in which UFH was not associated with significant survival benefit, administered at prophylactic or therapeutic doses while LMWH improved survival when given as prophylaxis [15].

The rate of thrombo-embolic complications was higher with the use of therapeutic LMWH compared to prophylactic LMWH, while the rate was similar between therapeutic and prophylactic UFH groups. This can be explained by the fact that in our institution we do not regularly monitor the anticoagulant effect of LMWH with anti-factor Xa levels which could lead to subtherapeutic levels [18,19]. This is further supported by a recent observation in which COVID-19 patients who were administered anti-Factor Xa–guided LMWH were achieving appropriate levels compared to weight-based approach [20]. There was no observed superiority of LMWH versus UFH, when these were compared at prophylactic and therapeutic doses respectively in preventing imaging confirmed macrovascular thromboembolic complications.

These findings should be interpreted with caution though. Due to the risk of viral contamination...
and the instability of critically ill COVID-19 patients that frequently precluded transportation, we did not routinely screen all our patients for the presence of subclinical PE or DVT and thus we have probably underestimated the true VTE rate. It has been shown in studies that adopted a more systematic screening approach that there was a higher VTE incidence compared to the ones that implemented imaging upon clinical suspicion only [21].

Previous studies have also shown that elevated D-dimer levels is a marker of COVID-19 hypercoagulability and disease severity, linked with worse mortality [22,23]. Our analysis found that the peak of the D-dimers matched the time of intubation and although there was no difference in the maximum D-dimer level between LMWH and UFH, regardless of AC dose, their levels significantly decreased after AC escalation, during the patients’ hospital course. Our findings were supported by another retrospective study in which the early implementation of AC was associated with down trending D-dimer levels and improved 30-day mortality in patients suffering from severe COVID-19 [24]. Based on the most updated NIH guidelines, therapeutic AC is currently recommended in adults with D-dimer levels above the upper limit, but only for those who require low-flow oxygen and do not require ICU-level of care [13].

Despite the survival benefit of AC administration to COVID-19 patients, a major contributor to morbidity and mortality is clinically significant bleeding. In our cohort when comparing LMWH to UFH, there was no difference in bleeding risk. This finding has been supported by studies that showed equivalent bleeding risk among patients receiving either LMWH or UFH [25], although others indicate that LMWH is associated with less risk for major bleeding, mostly attributed to more predictable anticoagulant response [26].

On the other hand, when comparing level of AC, we found that those who received therapeutic LMWH had higher bleeding complications compared to those on prophylactic, while there was
no difference in the UFH group between prophylactic or therapeutic doses. Although the
development of clinically significant bleeding with therapeutic AC is intuitive from a
physiologic perspective since higher doses can lead to impaired clotting, some studies have
shown no statistically significant difference in major bleeding events between prophylactic and
therapeutic AC in COVID-19 patients [27,28]. Nevertheless, our findings seem to be in line with
other studies in which therapeutic AC was associated with an increased risk of major bleeding
[30] although this observation could be due to a relative bias towards administering higher doses
of AC to sicker patients with higher D-dimer levels, [31], which was also the case in out cohort.
In our study population, the transfusion requirements were significantly higher in both LMWH
and UF therapeutic dose groups compared to prophylactic groups. Even though previous studies
have shown no difference in transfusion requirements with therapeutic AC [28,29], anemia
which is common in patients requiring ICU level of care, can be attributed not only to bleeding
events but also to decreased erythropoiesis by the cytokine-induced inflammatory status and the
frequent venipunctures [4].

Limitations
Our study has a retrospective, observational, opportunistic design based on a single center
experience, that was feasible in the setting of a new evolving phenomenon during which our
understanding of SARS-CoV2 was expanding. The fact that pulmonary embolism is common in
patients with severe COVID-19 infection and imaging was underutilized might have led to
underdiagnosis of thromboembolic complications. Our study did not include patients who did not
receive AC and thus we cannot make safe assumptions as to if some of the mortalities could be
attributed clearly to adverse effects of AC. The preferential administration of UFH to patients
with elevated creatinine could also introduce a potential selection bias. In our attempt to control this, we evaluated patients with acceptable renal function. Still, the small sample size precluded further conclusions in those who received prophylactic AC dose. Even though we found a statistically significant difference in the survival between LMWH and UFH in patients with creatinine <1.3, this comparison needs to be made with caution due to possibility for unobserved differences between the groups.

Conclusions. Among intubated critically ill COVID-19 ICU patients, therapeutic AC, with either LMWH or UFH, conveyed no survival benefit or greater organ support free days over prophylactic AC. AC with LMWH was associated with higher cumulative survival compared to AC with UFH.

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Table 1. Characteristics of patients that were on LMWH vs. UFH prophylactic vs. therapeutic level of AC.

|                          | LMWH           | UFH            | P-value |
|--------------------------|----------------|----------------|---------|
| **SOFA (mean ± SD)**     |                |                |         |
| prophylactic             | 5.8+0.23       | 4.09+0.95      | 0.04    |
| therapeutic              | 5.8+0.24       | 7.6+0.25       | 0.5     |
| **Max D-dimer for**      |                |                |         |
| prophylactic (mean ± SE)| 3472+458       | 3223+989       | 0.64    |
| therapeutic              | 12672+1618     | 11743+1470     | 0.67    |
| **Admit Creatinine for** |                |                |         |
| prophylactic (mean ± SE)| 0.99+0.11      | 1.34+0.25      | 0.14    |
|                          | Max Creatinine for prophylactic (mean ± SE) | Max Creatinine for therapeutic (mean ± SE) | p-value |
|--------------------------|---------------------------------------------|-------------------------------------------|---------|
| Admit Creatinine for     | 1.46+0.18                                   | 1.9+0.25                                  | 0.017   |
| therapeutic              |                                             |                                           |         |
| Max CRP, prophylactic    | 36.18+4.9                                   | 39.49+13.7                                | 0.97    |
| (mean ± SE)              |                                             |                                           |         |
| Max CRP, therapeutic     | 40.4+4.3                                    | 39.7+3.8                                  | 0.88    |
| (mean ± SE)              |                                             |                                           |         |
| Max Interleukin 6        | 218+70                                      | 1949+1134                                 | 0.003   |
| (Vivacor), prophylactic  |                                             |                                           |         |
| (mean ± SE)              |                                             |                                           |         |
| Max Interleukin 6        | 428+120                                      | 284+73                                    | 0.6     |
| (Vivacor), therapeutic   |                                             |                                           |         |
(mean ± SE)
Table 2. Multivariable analysis

| Variable         | Comparison level      | Hazard Ratio (95% CI.) | *P*-value |
|------------------|-----------------------|------------------------|-----------|
| Sex              | Male vs. Female       | 1.68 (1.01-2.78)       | 0.044     |
| Anticoagulation type | LMWH vs. UFH       | 0.47 (0.30-0.74)       | 0.001     |
| Age              | More than 70 vs. Less than 70 years old | 2.15 (1.36-3.39)       | 0.001     |
| SOFA             | More than 7 vs. Less than 7 | 1.33 (0.86-2.06)       | 0.188     |
| Steroids         | On vs. off steroids   | 1.50 (0.69-3.30)       | 0.303     |
Table 3. Comparing the complications of LMWH vs. UFH in prophylactic vs. therapeutic AC doses.

| Complications      | Prophylactic | Therapeutic | P- value |
|--------------------|--------------|-------------|----------|
|                    | UFH 11       | UFH 72      |          |
|                    | LMWH 70      | LMWH 65     |          |
| Thromboembolic     | 9%           | 18.06%      | 0.45     |
| UFH                | 4.2%         | 13.8%       | 0.051    |
| LMWH               |              |             |          |
| Bleeding           | 18.1%        | 31.9%       | 0.35     |
| UFH                | 4.2%         | 21.54%      | **0.002**|
| LMWH               |              |             |          |
| HIT                | 0            | 4.17%       |          |
| UFH                | 0            | 1.54%       |          |
| LMWH               |              |             |          |
| Received Transfusion| 36.3%      | 72.2%       | **0.0008**|
| UFH                | 18.5%        | 38.46%      | **0.002**|
| LMWH               |              |             |          |
| Condition                  | UFH (n=11) | LMWH (n=70) | p-value |
|---------------------------|------------|-------------|---------|
| Thromboembolic PE/DVT    | 18.06%     | 13.8%       | 0.5     |
| Arterial complications   | 9.7%       | 9.2%        | 0.9     |
| Bleeding                 | 31.9%      | 21.54%      | 0.17    |
| HIT                      | 4.17%      | 1.54%       | 0.36    |
| Received transfusion     | 72.2%      | 38.46%      | 0.001   |
| **Prophylactic UFH (n=11)** |           |             |         |
| Thromboembolic            | 9%         | 4.2%        | 0.49    |
| Bleeding                  | 18.1%      | 4.2%        | 0.075   |
| HIT                       | 0%         | 0%          |         |
| Received transfusion      | 36.3%      | 18.5%       | 0.17    |
Figure 1. Patient selection algorithm
Figure 2. AC with LMWH is associated with significantly higher cumulative survival compared to UFH based AC, regardless of AC level, prophylactic or therapeutic. There was no difference in cumulative survival when comparing prophylactic UFH to therapeutic UFH. Similarly, there was no difference in cumulative survival when comparing prophylactic LMWH to therapeutic LMWH.
Figure 3. Evolution of the critical inflammation markers and organ function laboratory values over the ICU period in COVID-19 intubated patients treated by UFH (green, n = 83) and LMWH (blue, n = 134), regardless of AC level.