**Peer Review File**
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**Reviewer A**

The study provides important data on advanced mechanical circulatory support strategies in cardiogenic shock patients. I believe that the following comments will improve the strength of the manuscript.
My comments:

**Comment 1:** The main point that should be clarified in the manuscript is whether the v-a ECLS patients were "converted" to an isolated Impella 5.0 support or underwent an "upgrade" to an ECMELLA approach. The term "upgrade" in this setting should be referred to as an "ECMELLA" only. ECLS explantation with a concomitant Impella implantation is NOT an upgrade (Line 58, 347).
**Reply 1:** Thank you for this important comment, you have raised a very important and confusing point, we have made the necessary changes to the title, the abstract and sentences concerned. See highlighted update.
**Changes in the text:** (title, abstract and manuscript see highlighted multiples corrections)

**Comment 2:** Please use the terms v-a Extracorporeal Life Support (ECLS) and ECMELLA. The term VA-ECMO is not technically correct anymore.
**Reply 2:** We thank reviewer A for this point. VA-ECMO was replaced by ECLS all the paper long. Venoarterial extracorporeal membrane oxygenation was also changed to Extracorporeal Life Support
**Changes in the text:** See highlighted multiple changes

**Comment 3:** Line 35: the sentence "INTERMACS 1 patients in cardiogenic shock requiring CPR" is bulky and overloaded with synonyms, please rephrase and simplify.
**Reply 3:** Thank you for this remark. The sentence is rewritten as follow hoping this will be appreciated by reviewer 1:
**Changes in the text: (Page 2 line 35)** Venoarterial extra corporeal life support (ECLS) is the treatment of choice of INTERMACS 1 patients, but left ventricular (LV) overload is a complication of ECLS. Unloading the LV by adding Impella 5.0 to ECLS in ECMELLA configuration is recommended only in patients with acceptable prognosis. We investigated whether serum lactate level, a simple biological parameter, could be used as a marker to select candidates for bridging from ECLS to ECMELLA.

**Comment 4:** Line 38: "weaning and upgrading to an alternative MCS" is NOT mandatory. Please rephrase.
**Reply 4:** We thank reviewer A for this improvement. Please refer to the previous point

**Changes in the text: (Page 2 line 35)** Venoarterial extra corporeal life support (ECLS) is the treatment of choice of INTERMACS 1 patients, but left ventricular (LV) overload is a complication of ECLS. Unloading the LV by adding Impella 5.0 to ECLS in ECMELLA configuration is recommended only in patients with acceptable prognosis. We investigated whether serum lactate level, a simple biological parameter, could be used as a marker to select candidates for bridging from ECLS to ECMELLA.

**Comment 5:** I would recommend to directly focus on need for LV unloading in ECLS in the abstract and to shorten the background part in abstract.
**Reply 5:** Thank you for the clarification request. The answer provided here is a combo with the previous requests
**Changes in the text: (Page 2 line 35)** Venoarterial extra corporeal life support (ECLS) is the treatment of choice of INTERMACS 1 patients, but left ventricular (LV) overload is a complication of ECLS. Unloading the LV by adding Impella 5.0 to ECLS in ECMELLA configuration is recommended only in patients with acceptable prognosis. We investigated whether serum lactate level, a simple biological parameter, could be used as a marker to select candidates for bridging from ECLS to ECMELLA.

**Comment 6:** Line 45: please mention that patients were on ECLS support, and they were NOT "converted" to Impella support but "underwent an Impella implantation".
**Reply 6:** Thank you for the clarification request. Your interesting review has been taken into account)
**Changes in the text:** Whenever requested, "bridge" was replaced by "adding", see highlighted corrections at various place.

**Comment 7:** Line 81: please write down which "specific conditions you have meant".
The paragraph has been reworded and corrected
**Changes in the text: page 2 line 42, 43):** Forty-one consecutive INTERMACS 1 patients under ECLS were upgraded to ECMELLA using Impella 5.0 pump implantation to unload the left ventricle and were followed-up for 30 days.

**Comment 8:** Line 88: please concretize which 30% of ECLS patients require a mandatory weaning and upgrade?
**Reply 8:** This sentence corresponded to the conclusion of the cited article, but because of inconsistent results in the literature, we decided to skip this sentence.
**Changes in the text:** page 3 line 80 is now: In rescued INTERMACS 1 patients, ECLS is the treatment of choice as a bridge to long-term device support, transplantation or recovery (2). One of the major complications of ECLS is that it increases left ventricular overload

**Comment 9:** Line 92-93: Impella 5.0 is NOT a first line therapy in INTERMACS 1 patients, expectation of a LV recovery before MCS start is a pure speculation. CPR patients are also INTERMACS 1 and might have high chances for recovery; however, require a rapid ECLS implantation. Please rephrase.

**Reply 9:** Thank you for your remark, we have rephrased the sentence and emphasized on the left ventricle unloading effect of impella 5.0
**Changes in the text: page 3 line 88 is rephrased as follow:** Its implementation in addition to ECLS, i.e. ECMELLA, has been described to counteract ECLS related complications, mainly the left ventricle overload that strongly affect the outcome (4,5).

**Comment 10:** Please clarify in the section statistical analysis, how the cut-off for lactate was found.
**Reply 10:** We thank reviewer 1 § "statistics" was unclear. We calculated the performance of lactate level and troponin concentration (sensitivity and specificity), from which we constructed a Receiver Operator Characteristic (ROC) curve where cut off shall be the point, which possesses, the maximum sensitivity and specificity values.
**Changes in the text: page 6 line 176 was added:** "Thus for lactate level and troponin concentration, the best cutoffs were points on the curve with minimum distance from the left-upper corner of the unit square; and the point where the Youden's index is maximum."

**Comment 11:** Line 194: please provide the percentage of patients with an ICMP.
**Reply 11:** Thank you for your request, which is now updated in the manuscript.
**Changes in the text: page 6 line 190**. "Etiologies of cardiogenic shock leading to emergency ECLS implantation were mostly related to acute coronary syndrome (n = 18, 44%) and decompensated chronic heart disease (n=12, 29%, table 1)."

**Comment 12:** Line 200: please explain the significant differences between the low flow duration in asystole and VT/VF. In hospital vs external CPR?
**Reply 12:** Both (asystole and shockable rhythm) had a no-flow of 0 ± 1 min and a low-flow 42 ± 43 min. The sentence should be understood like that. Unfortunately, we don't have detailed information for each heart rhythm. We have rephrased the text as follow:
**Changes in the text: page 6 line 193**. Cardiac arrest was reported in 63% of the patients whether in asystole or shockable rhythm (ventricular tachycardia/fibrillation). For both, the no flow was of 0 ± 1 min and the and low flow was 42 ± 43 min (table 1).

**Comment 13:** L 211: please use term preoperative invasive ventilation.
**Reply 13:** We thank reviewer 1 for this relevant point and have updated the text
**Changes in the text: page 7, line 206**: preoperative invasive ventilation

**Comment 14:** L 263: please rephrases the bulky phrase on 30-day in-hospital mortality.
**Reply 14:** We have reworded the sentence and taken into account your relevant comment
**Changes in the text: page 9, line 261**: "In our small retrospective study, among the 41 patients upgraded to ECMELLA, in hospital mortality remains high (61% ; n=25)."

**Comment 15:** L 283: please provide the number of patients died on support (not only the percentage.

**Reply 15:** We took into account this crucial point raised by reviewer 1 and updated the manuscript subsequently.
**Changes in the text: page 9 line 281:** "Thus, eight patients were able to fully recover after sequential ECLS followed by Impella 5.0 pump implantation with no extra support, while 25 died.

**Comment 16:** L 289-291, L 340: mean of 31h is not a short period. Schrage et al (PMID 33032450), where it was demonstrated that the delay of LV unloading in ECLS patients of more than 2h negatively impacts the survival. Therefore, 31h without LV unloading is a long period. Please include this point also in the discussion as a potential reason for poor outcomes (delayed unloading).
**Reply 16:** Reviewer 1 has pointed-out one crucial limitation of our results and we really appreciate this important paper highlighting detrimental outcomes of delay LV unloading. We of course updated our manuscript in discussion section but also in limitation. However, we wanted to apologize because Impella 5.0 was implanted 9h after ECLS and not 31 hours. Again, we acknowledge this is quite late.
**Changes in the text: page 9 line 289: "**Here, the Impella 5.0 pump was implanted implanted 9 [0;30] hours (table 1) after ECLS. Optimal timing for left ventricle unloading under ECLS still controversial. However, Scharge et al (20) demonstrated that the delay of LV unloading in ECLS patients of more than 2 hours negatively impacts the survival."
**Changes in the text: page 11 line 342 to 346: "**We already mentioned that delaying LV unloading in INTERMACS 1 patients beyond 2 hours might have a detrimental effect on mortality as reported by Schrage et al. (20), meaning that outcomes are not only driven by lactate level.

**Comment 17:** Please include in the discussion the point that cut-off values for lactate in patients before MCS (Study from Nersesian et al.) and on ECLS support are similar and a valuable tool both before and on support.
**Reply 17:** The paper is updated according to his relevant suggestion from Reviewer 1 we wanted to thank
**Changes in the text: Page 1, line 329 to 331:** Nersesian et al. identified a cut-off of 8 mmol/L for lactate level before and on ECLS support to predict a poor outcome (4). This threshold was similar in our work, suggesting that Impella 5.0 pump implantation should not be used in patients on ECLS with a serum lactate level of > 7.9 mmol/L.

**Comment 18:** In study limitation small cohort size should be also mentioned.
**Reply 18:** Thank you for this relevant limitation suggested by reviewer 1
**Changes in the text: Page 11, line 350:** First, we would like to mention that is small cohort size.

**Comment 19:** Table 3: "brain death" please try to differentiate: brain death related to tMCS (ICB) and palliation due to non-ECLS related issues.

**Reply 19:** We thank reviewer A for this clarification. We dichotomized in table 3 death related to ECLS and non-ECLS related.
**Changes in the text:** Corrected in page 15, table 3

**Comment 20:** Figure 2: please use a time referral in the KM-curve ("days since Impella implantation". Please add CI-intervals to the graphs.
**Reply 20:** This important information was updated in graph 2.
**Changes in the text: Page 17, Figure 2:**
CI : 3,4 [2,3 – 23,5]
Patients at risk were added as requested.

**Reviewer B**

This is a well-written manuscript dealing with a very interesting research question, which is the selection of patients with acute cardiogenic shock, who are suitable candidates for an Impella 5.0 upgrading of their extracorporeal right ventricular support via VA-ECMO. Please pay attention to the following questions and comments pertaining to your manuscript:

**Comment 1:** Abstract, Lines 58-59: an upgrade from VA-ECMO to Impella 5.0 is relevant if the serum lactate level is ≤ 7.9 mmol/L. I suggest to reform this sentence like: an upgrade from VA-ECMO to ECPELLA, in order to avoid misunderstanding that VA-ECMO was explanted and Impella 5.0 was the only right ventricular supporting system.
**Reply 1:** We thank you for pointing out the inappropriateness of this paragragh and the lack of background, this has been corrected. This crucial point was mentioned by reviewer A and we appreciate if you can refer to corrections suggested by this reviewer. The use of the term ECMELLA and ECLS was required of us by the editor
**Changes in the text:** all along the manuscript, please see highlighted corrections.

**Comment 2:** Results, Lines 234-235: 25 patients died from multiple organ failure (10 patients), brain death (9 patients), major bleeding (3 patients) and multiorgan failure (3 patients): multiple organ failure and multiorgan failure is the same cause of death. Please correct this point accordingly.
**Reply 2:** We thank you for mentioning data discrepancy between table 3 and the manuscript. We corrected theses errors, and simplified a bulky sentence. The manuscript is updated end rephrased as follow.
**Changes in the text: page 8 line 228:** Among the 25 patients of the non-survivor group, 10 died from multiple organ failure, nine for brain death with ECMELLA discontinuation, and 3 patients for major bleeding (table 3). Four patients weaned from ECMELLA after long term LVAD implantation died from right ventricular failure. Among the 16 patients who survived, two patients were transplanted, three patients

were weaned from ECMELLA, one converted to total artificial heart implantation and two bridged to long-term LVAD implantation, while 11 recovered.

**Comment 3:** Results, Line 251: predictors of events. You probably mean predictors of death. Please become more specific with the term "events".
**Reply 3:** We thank you reviewer 2, this mistake was corrected.
**Changes in the text: page 8 line 246:** In univariate analysis, acute coronary syndrome, cardiac arrest before ECLS implantation, serum lactate > 7.9 mmol/L and troponin > 2700 UI were independent predictors of death.

**Comment 4:** Discussion, Line 338: with a majority of acute myocardial infections. You probably mean with a majority of acute myocardial infarction.
**Reply 4:** Thank you. This error was corrected.
**Changes in the text: page 11 line 355** is as follow: Furthermore, our population was heterogeneous at baseline, with a majority of acute myocardial infarction and few chronic left ventricular dysfunctions.

**Reviewer C**

The manuscript evaluates lactate as a prognostic parameter in patients with cardiogenic shock supported with VA-ECMO and escalated to ECPELLA. At some stages the English could be improved but the overall text reads fluently. The topic is of interest.

My comments:

Major:
**Comment 1:** In a population with 63% of patients resuscitated from cardiac arrest and 41 min of mean low flow time, I would consider the possibility that lactate was a marker of longer resuscitations which affected outcomes. This is also suggested by the baseline characteristics in which the low-flow time for survivors is much shorter. I would be very careful with the conclusions based on these findings since the results could potentially not be applicable for patients that are not resuscitated from cardiac arrest. Maybe the authors could do a separate analysis for resuscitated and non-resuscitated patients, although the small numbers will make this difficult.
**Reply 1:** We thank reviewer 3 for this important point. We do agree that there many confounding factors with mortality in this manuscript like cardiac arrest, duration of low-flow, acute coronary syndrome that may have change the lactate level at baseline. However, in our manuscript we should mentioned that lactate level was that one measures just before Impella 5.0 implantation and not at baseline with a mean of 9 hours when upgrading to ECMELLA. We thought that lactate level at the time of implantation is more a marker of a persistent poor condition than an initial presentation. Thus, time varying lactate level could be more relevant than baseline or at 5.0 Impella implantation to be correlated to outcomes. Second, outcomes were corrected to all

conditions that were significantly different between survivors and non-survivors, i.e. cardiac arrest, duration of low flow, acute coronary syndrome and still lactate level after multivariate analysis remain significantly linked to mortality.
**Changes in the text: page 11 line 336**: this paragraph is added "Beside, lactate level has confounding factors with mortality in this manuscript like cardiac arrest, duration of low-flow, acute coronary syndrome that may have change the lactate level at baseline. However, in our manuscript we should mentioned that lactate level was that one measures just before Impella 5.0 implantation and not at baseline with a mean of 9 hours when upgrading to ECMELLA. We thought that lactate level at the time of implantation is more a marker of a persistent poor condition than an initial presentation. Thus, time varying lactate level could be more relevant than baseline or at 5.0 Impella implantation to be correlated to outcomes. Second, outcomes were corrected to all conditions that were significantly different between survivors and non-survivors, i.e. cardiac arrest, duration of low flow, acute coronary syndrome and still lactate level after multivariate analysis remain significantly linked to mortality.

**Comment 2:** Why were the prognostic scores that are commented upon, not calculated for the patients in the study. By showing that they are not significantly different, the authors could make their point in the discussion more valid.
**Reply 2:** Thank you for this relevant update. Unfortunately, and due to missing data we were not able to add an alternative score in our manuscript and we do apologize for these limitations.

Minor:
**Comment 1:** Abstract: "delayed return of spontaneous circulation". I would change this term. ROSC is mainly used to describe circulation in case of CPR. This could be misleading.
**Reply 1:** We would like to thank reviewer 3 for this mistake. We have change the abstract according to other reviewers and "delayed return of spontaneous circulation" does no longer exist in the abstract section.
**Changes in the text: page 2 line 35 is rephrased to:** Venoarterial extra corporeal life support (ECLS) is the treatment of choice of INTERMACS 1 patients, but left ventricular (LV) overload is a complication of ECLS. Unloading the LV by adding Impella 5.0 to ECLS in ECMELLA configuration is recommended only in patients with acceptable prognosis. We investigated whether serum lactate level, a simple biological parameter, could be used as a marker to select candidates for bridging from ECLS to ECMELLA

**Comment 2:** P3: although I agree personally that early ECMO weaning with the help of a pVAD is probably useful, we have no good data to support this at this stage. I would be careful with this statement especially when referring to a review article.
**Reply 2:** We thank reviewer 3 for this relevant information. We updated or manuscript.

**Changes in the text: page 3 line 89 is** added: PVAD is an alternative but we have no good data to support this at this stage.

**Comment 3:** Time to 5.0 Impella is long (31 h) if the intent was unloading as is suggested by the methods paragraph that describes the indication. Based on eg, the study by Schrage in circulation 2020, earlier unloading could result in more benefit and this could have changed the results. Can the authors comment on this?
**Reply 3:** Reviewer 1 has pointed-out one crucial limitation of our results and we really appreciate this important paper highlighting detrimental outcomes of delay LV unloading. We of course updated our manuscript in the discussion section but also in limitation. However, we wanted to apologize because Impella 5.0 was implanted 9h after ECLS and not 31 hours. Again, we acknowledge this is quite late.
**Changes in the text: page 9 line 288: "**Here, the Impella 5.0 pump was implanted 9 [0;30] hours (table 1) after ECLS. Optimal timing for left ventricle unloading under ECLS still controversial. However, Scharge et al (20) demonstrated that the delay of LV unloading in ECLS patients of more than 2 hours negatively impacts the survival."
**Changes in the text: page 11 line 344 to 346: "**We already mentioned that delaying LV unloading in INTERMACS 1 patients beyond 2 hours might have a detrimental effect on mortality as reported by Schrage et al. (20), meaning that outcomes are not only driven by lactate level.

**Comment 4:** The patients are much younger than the typical population. Can the authors comment on this?
**Reply 4:** As a candidate for heart transplantation, only young patients are candidates to aggressive ECLS and Impella management in our institution. Impella 5.0 is costly and has other side effects. Older patients are translated intra-aortic balloon pump or transseptal unloading.

**Reviewer D**

This study analysis the INTERMACS 1 patients that received mechanical circulatory support with VA-ECMO and Impella 5.0 pump. Based on the experience of the single center, retrospective and observational studies were conducted. The author compared demographic, clinical, biological parameters of survivor and non-survivor who underwent VA-ECMO and Impella 5.0 pump implantation. After multivariable cox regression analysis, authors suggested that the lactate level of >7.9mmol/L was an independent predictor of mortality. According to these findings, lactate level can be helpful to decision making whether that patient need upgrade from VA-ECMO to impella 5.0 or not. I agree that lactate level is crucial in the treatment of cardiogenic shock patients, but I have some concerns about these results and interpretation.

**Comment 1:** First, differences in baseline characteristics between survivors and non-survivors didn't be adjusted. The group of survivors had less risk factors than the group of non-survivors. And etiology and status at VA-ECMO implantation has some

differences. A large portion of non-survivor groups were acute coronary syndrome, and the proportion of cardiac arrest or low flow time was higher than that of survivors. These results implicate that the severity of cardiogenic shock was different at the baseline and lactate level may be affected by these multiple factors. Therefore, there has a possibility of the existence of other confounding variables.

**Reply 1:** We thank reviewer D for this point and apologize if our statistics were unclear. As mentioned in the manuscript, the cox proportional method was performed in parameters were p was less than 0.05 between survivors and non survivors in a stepwise process starting with uni- then multivariate analysis meaning that multivariate Cox proportional hazards method tested how dichotomized lactate level influenced death adjusted to age (p<0,014, table 1), sex (p<0,019, table 1), cardiac arrest (p<0,007,table 1), acute coronary syndrome (p<0,037, table 1). Hypercholesterolemia which was also significant did not enter the model since we considered it futile and not determinant for the result. When we entered "low flow", lactate level was still significant as indicated in the following table.

**Variables in the Equation**

| | B | SE | Wald | df | Sig. | Exp(B) | 95,0% CI for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| LACTDICH2 | 1,171 | ,584 | 4,021 | 1 | ,045 | 3,224 | 1,027 | 10,123 |
| AGE | ,024 | ,028 | ,690 | 1 | ,406 | 1,024 | ,968 | 1,082 |
| SEXE | -,972 | ,726 | 1,794 | 1 | ,180 | ,378 | ,091 | 1,569 |
| Acute coronary syndrom | ,517 | ,683 | ,574 | 1 | ,449 | 1,677 | ,440 | 6,394 |
| Cardiac arrest | ,850 | 1,092 | ,605 | 1 | ,437 | 2,339 | ,275 | 19,904 |
| LOWLOWmin | ,412 | ,262 | 2,475 | 1 | ,116 | 1,510 | ,904 | 2,523 |
| TROPODICH4000 | ,873 | ,605 | 2,078 | 1 | ,149 | 2,393 | ,731 | 7,839 |

In conclusion, when adjusted to many factors including age and sex, lactate level remains statistically linked to prognosis. CI = 3,2 [1,0 – 10,1]

**Changes in the text: page 8 line 249:** However, in multivariate analysis adjusted for age and sex as well as others confounding factors,

**Comment 2:** Second, the author dichotomized patients by lactate levels and results were shown in figure 2. However, major difference of the mortality between two groups occurs in initial of graph. The overall slope of survival between two groups looks similar. These results are questionable that really lactate level can be independent predictor of mortality without selection bias. Because this study was a retrospective data of single center, it is difficult to distinguish whether c

**Reply 2:** We agree with this important point. Mortality is mainly driven in the early days following ECMELLA implantation. In a “a priori” medical decision making, lactate level is more a determinant of the severity of he disease meaning that patients having concentration above 7.9 should not be upgraded to ECMELLA since the prognosis is determined by the MOF.

**Reviewer E**

General

**Comment 1:** This article aims to identify suitable patients with INTERMACS-1, already supported with VA-ECMO, who need an upgrade with Impella 5.0, using serum lactate levels. This is relevant work although similar data has been published before. According to the authors, patients with lactate levels > 7.9 mmol/l are not deemed to be suited for an upgrade with Impella. Conclusions are based on a follow-up of 30 days and especially based on the differences between survivors and non-survivors. Interesting view would be if neurological outcomes and recovery could be included in this analysis, as quality of life is essential as well. Has this been performed by the authors? Or were there reasons not performing these analyses? More over only patients upgrade to Impella 5.0 were considered. Did the centre treat other patients with IABP or with smaller access Impella like CP. Patients treated with only ECMO for same indication, either good survivors or too bad for upgrade. Please include these in figure 1.

**Reply 1:** We thank reviewer 5 for this very relevant and important point-of-view. Unfortunately, this paper is by essence retrospective with a lot of missing data and paid less attention to neurological prognosis. We do apologize for this limitation and we will do our best in the future to take into account this major point. Regarding QOL for those who are alive, we recently developed a close 3-month follow-up of patients in collaboration with intensive care physician. These important data will be available in a prospective work.

As far as we are concerned, Impella 5.0 is the preferred unloading technique for young patient in our institution. However, we alternatively use IACB, inotropic drugs support, transseptal unloading as well as diuretic and if needed hemodialysis (see table 3). The paper is only dedicated to Impella 5.0 in addition to ECLS. With never used Impella CP.

Specific

**Comment 1:** Certain characteristics with importance regarding ventricular overload, survival and multi-organ failure are currently lacking in this article:

- Amount of cardiac support provided by MCS device, especially before implantation of the Impella device.

**Reply 1:** We thank reviewer 5 pour this request that is really relevant

**Changes in the text:** **Page 14 line 378, table 2:** inotropic support is provided in table 2 in a binary approach. IABC is also reported in table 2.

**Comment 2:** Duration of MCS device support (are patients decanulated at all?, or immediately at upgrade?
**Reply 2:** Thank you for this relevant remark. It was confusing for other reviewer and we apologize for this. The paper is rewritten to clarify that Impella 5.0 was implanted on top of ECLS, in an ECMELLA configuration meaning the patient wasn't decannulated, unless it was requested by end-of-life or bridge to recovery/transplantation/LVAD.
The time between ECLS and Impella 5.0 implantation was 9.0 [0-30] hours.
showever table 2 describes the characteristics of the patients **AT THE TIME of implantation** of the impella 5.0 in patients undergoing ECLS.
**Changes in the text:** see changes highlighted in the manuscript

**Comment 3:** Duration of mechanical ventilation During ECLS and ECMELLA,
**Reply 3:** All the patients were under mechanical ventilation during ECLS of ECMELLA.
Duration of mechanical ventilation were added in **table 3**
**Changes in the text: (Page 15 line 386) table 3**

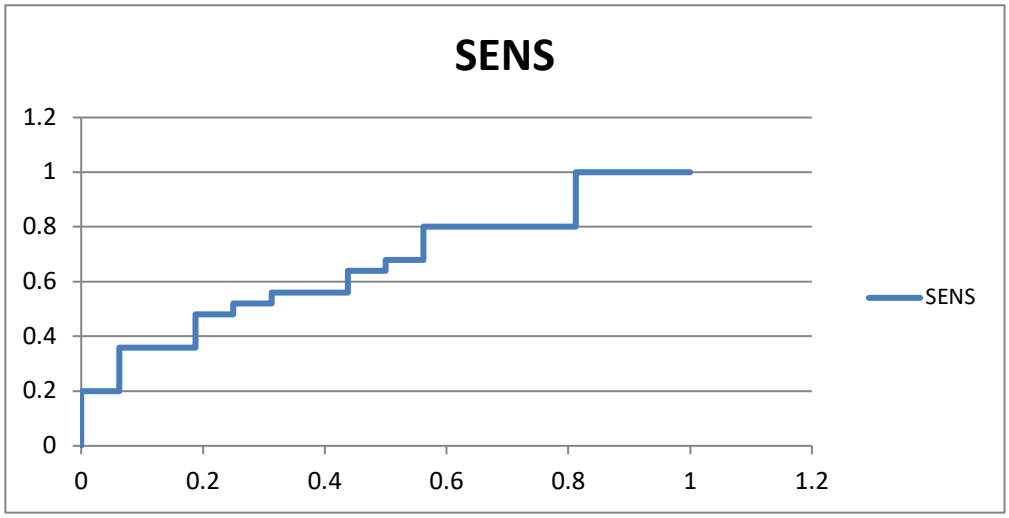
**Comment 4:** - Need for dialysis
**Reply 4:** 13 of the 41 ECMELLA patients needed dialysis in the ICU, However, in table 2 describing patients characteristics **AT TIME of Impella 5.0 implantation** creatinine levels were the only reliable data that we have chosen to describe. The exact time to stard dialysis in the first day of ECMELLA are not really known in this retrospective study. We described the need for dialysis in table 3 showing the in-hospital outcomes as binary data. We do apologize if this data is missing
**Changes in the text: (Page 15 line 386) table 3**

**Comment 5:** Acute coronary syndrome is present in almost 50% of the patients included in this study. First, does this group consists of STEMI, NSTE-MI and unstable angina? If so, what is the distribution? Second, are these patients all successful revascularized?
**Reply 5:** Thank you for this relevant point that may have impacted outcomes. **In table 1** Acute coronary syndrome was found in 44% of the patients, this group consisted of STEMI with a normal distribution between survivors and non-survivors. Non-STEMI and unstable Angina, were not reported. Coronarography angiogram (CAG) and percutaneous coronary intervention (PCI) were described in table 3. Successfulness of revascularization is a missing data.
**Changes in the text: (Page 15 line 386) table 3**

**Comment 6:** Cardiac arrest was reported in 63% of patients. Please specify if this was OHCA, IHCA, if VA-ECMO was initiated after ROSC or as eCPR.
**Reply 6:** Thank you for this remark, in our center, we do not initiate extra-hospital ECLS. In-hospital cardiac arrest who benefited from salvage ECLS were initiated as eCPR.

**Comment 7:** Why did the authors not investigate to time variance of Lactate. High lactate within 24 hours is different from 216 hours post ECMO. The author note in the literature this has been proven to be a better predictor.
**Reply 7:** We did not look at the clearance of lactate level because we had a lot of missing data. We thank Reviewer E because we believe that time-varying lactate concentration is better than an isolated assessment of the parameter at baseline or right before Impella 5.0 implantaion. When ECMELLA was implanted several days after VA-ECLS, time-varying lactate concentration was sometimes available, but for those patients with quick or immediate implantation of ECMELLA, those data were not available. Thus, we disregard this very important parameter.

**Comment 8:** The authors should investigate Lactate as a continuous value. Just the median is insufficient for clinical decisions. Please include ROC curves for lactate to determine optimal cut-off.
**Reply 8:** Lactate concentration was not investigated as a continuous variable. For the clinical decision-making we preferred to identify a threshold, which above it, the prognostic is worse. The ROC curve is included below and we used C-STAT to identify the best cut-off.




**Comment 9:** Why were age and sex not included in the multivariate analysis? These seem important for outcome and clinical decisions.
**Reply 9:** We thank reviewer E for this point and apologize if our statistics were unclear. As mentioned in the manuscript, the cox proportional method was performed in parameters were p was less than 0.05 between survivors and non-survivors in a stepwise process starting with uni- then multivariate analysis meaning that multivariate Cox proportional hazards method tested how dichotomized lactate level influenced death adjusted to age (p<0,014, table 1), sex (p<0,019, table 1), cardiac arrest (p<0,007,table 1), acute coronary syndrome (p<0,037, table 1). Hypercholesterolemia which was also significant did not enter the model since we considered it futile and not determinant for the result. When we entered “low flow”, lactate level was still significant as indicated in the following table.

**Variables in the Equation**

| | B | SE | Wald | df | Sig. | Exp(B) | 95,0% CI for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
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| AGE | ,024 | ,028 | ,690 | 1 | ,406 | 1,024 | ,968 | 1,082 |
| SEXE | -,972 | ,726 | 1,794 | 1 | ,180 | ,378 | ,091 | 1,569 |
| Acute coronary syndrom | ,517 | ,683 | ,574 | 1 | ,449 | 1,677 | ,440 | 6,394 |
| Cardiac arrest | ,850 | 1,092 | ,605 | 1 | ,437 | 2,339 | ,275 | 19,904 |
| LOWLOWmin | ,412 | ,262 | 2,475 | 1 | ,116 | 1,510 | ,904 | 2,523 |
| TROPODICH4000 | ,873 | ,605 | 2,078 | 1 | ,149 | 2,393 | ,731 | 7,839 |

In conclusion, when adjusted to many factors including age and sex, lactate level remains statistically linked to prognosis. CI = 3,2 [1,0 – 10,1]

**Changes in the text: page 8 line 249:** However, in multivariate analysis adjusted for age and sex as well as others confounding factors,

**Comment 10:** Conclusions in this article are based on 30-days follow-up time, in which 90% of the patients with lactate levels >7.9 mmol/l have died versus approximately 10% with lactate levels <7.9 mmol/l. Although mean duration of hospital stay is 28 days, the standard deviation is quite broad with 38 days. Therefore, how are the numbers of in-hospital deaths? Are there patients discharged from hospital admission and died afterwards? If so, what was there destination of discharge and was the reason of death?

**Reply 10:** This is an important point and we would like to thank reviewer E. Outcomes were evaluated at 30-day follow-up with results presented here. For those who were alive, discharge was at a mean of 28 days but sometimes prolonged, particularly if ECMELLA was used as bridge for transplantation of LVAD implantation. After 30 days, mortality rate remains elevated at a rate of 61%.

**Comment 11:** The authors are limited in the discussion on literature of Impella CP or IABP as alternatives. These have the similar outcome.

**Reply 11:** As far as we are concerned, Impella 5.0 is the preferred unloading technique for young patient in our institution. However, we alternatively use intra-aortic balloon pump, (see table 2). The paper is only dedicated to Impella 5.0 in addition to ECLS. We never used Impella CP in intermacs 1 patients, it is a team choice.

**Comment 12:** Table 1. BMI shows a p-value of 0.58, which is non-significant. Should be noted as NS, according to the other non-significant variables?
**Reply 12:** Thank you for pointing out this mistake; it has been corrected in table 1.
**Changes in the text: page 13 line 375:** correction

**Comment 13:** Table 3. Brain death occurred to 8 patients of the total number of 41 patients; however, in the non-survivor group, consisting of 25 patients and derived from the 41 included patients, 9 patients suffered from brain death; that seems inconsistent.
**Reply 13:** Thank you for pointing out this mistake; it has been corrected in table 3. There are 8 brain deaths.
**Changes in the text: page 15 line 386:** correction

**Comment 14:** Table 4: ACS with a p-value of 1.78 seems an error.
**Reply 14:** Thank you for pointing out this mistake; it has been corrected in table 4. P = 0.78.
**Changes in the text: page 16 line 397:** correction in table 4.