Soluble suppression of tumorigenicity 2 as outcome predictor after cardiopulmonary resuscitation: an observational prospective study

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Prognostication after cardiopulmonary resuscitation (CPR) is complex. Novel biomarkers like soluble suppression of tumorigenicity 2 (sST2) may provide an objective approach. A total of 106 post-CPR patients were included in this single-center observational prospective study. Serum sST2 levels were obtained 24 h after admission. Individuals were assigned to two groups: patients below and above the overall cohort’s median sST2 concentration. Primary outcome was a combined endpoint at 6 months (death or Cerebral Performance Category > 2); secondary endpoint 30-day mortality. A uni- and multivariate logistic regression analysis were conducted. Elevated sST2-levels were associated with an increased risk for the primary outcome (OR 1.011, 95% CI 1.004–1.019, p = 0.004), yet no patients with poor neurological outcome were observed at 6 months. The optimal empirical cut-off for sST2 was 46.15 ng/ml (sensitivity 81%, specificity 53%, AUC 0.69). Levels above the median (> 53.42 ng/ml) were associated with higher odds for both endpoints (death or CPC > 2 after 6 months: 21% vs. 49%, OR 3.59, 95% CI 1.53–8.45, p = 0.003; death after 30 days: 17% vs. 43.3%, OR 3.75, 95% CI 1.52–9.21, p = 0.003). A positive correlation of serum sST2 after CPR with mortality at 30 days and 6 months after cardiac arrest could be demonstrated.

Prognostication after cardiac arrest (CA) remains a multi-faceted challenge in modern intensive care medicine. Various clinical parameters, neurophysiological tests, as well as imaging and laboratory findings can be included in the decision-making process1. Novel cardiovascular biomarkers are the subject of current research and could provide an objective approach in prognostication after successful cardiopulmonary resuscitation (CPR). Current guidelines emphasize uncertainty regarding ultimate cut-off values for conventional neuroprognostication markers such as neuron-specific enolase (NSE) and S-100B protein2. Furthermore, the use of glial fibrillary acidic protein, serum tau protein or neurofilament light chain remains subject of controversial debate3.

Suppression of tumorigenicity 2 (ST2) is assumed to play a role in inflammatory T-cell mediated processes3. In recent years, the importance of the ST2-/IL-33 axis has been repeatedly investigated for patients with different cardiovascular or inflammatory diseases4–6. Various pro-inflammatory but also protective effects (especially regarding cardiovascular remodeling) have been attributed to these signaling pathways4,7. Significantly divergent biomarker concentrations have been shown to be prognostically relevant for various disease entities8–11.

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Data on sST2-levels after resuscitation are scarce, hence further investigation is reasonable and necessary. Ristagno and colleagues demonstrated that sST2 and circulating, complement-activating pattern-recognition receptor Pentraxin 3 (PTX3) were independently associated with mortality and multiorgan failure immediately after ICU admission in patients in the FINNRESUSCI collective. In addition, sST2-levels 48 h after admission were found to be independently associated with ICU mortality. In the past, we have investigated the sST2/IL-33 axis in different cardiovascular diseases and gained good experience with sST2 as a powerful indicator of generalized inflammation as well as a prognostic parameter. In our single-center observational study, we prospectively investigated the prognostic relevance of the sST2/IL-33-axis, measured 24 h after cardiopulmonary resuscitation to create thesis-generating data for large future studies.

Patients and methods

Study subjects. This observational, prospective, single-center study was conducted at the medical ICU at the Paracelsus Medical University Salzburg between December 2018 and March 2020. All patients with a minimum age of 18 years admitted after cardiopulmonary resuscitation (both out-of-hospital and in-hospital CA) with a minimum stay of 24 h were included, after exclusion of traumatic cardiac arrest. Pregnant patients were excluded from the study. The process of patient enrollment is shown in Fig. 1. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice and approved by the local ethics committee (Ethikkommission Land Salzburg 415-E/2408/8-2018). Written informed consent was obtained; in deceased patients or patients with poor neurological outcome, informed consent was obtained from next of kin when applicable. All patients received optimal standard care regardless of study participation. Laboratory tests and imaging studies were performed independently of study inclusion according to local practice guidelines. Left ventricular ejection fraction was determined by echocardiography by the attending physician immediately after admission to the ICU. It was determined to be “normal” (in males: 52–72%, in females 54–74%), “mildly abnormal” (in males: 41–51%, in females 41–53%), “moderately abnormal” (in both sexes 30–40%) and “severely abnormal” (in both sexes < 30%) according to the 2015 ASE Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults. Medical personnel were blinded to the determined sST2-values. Follow-up examinations included neurologic assessment via Cerebral Performance Category (CPC) and were performed by telephone at 30 days and 6 months.

Laboratory analysis. Blood samples for the study were collected 24 h after ICU admission along with routine probes. Serum tubes were used for analysis of novel cardiovascular biomarkers and centrifuged thirty minutes after blood collection. Thereafter, the supernatant was frozen at minus 20 °C. Within 1 month after collection, laboratory samples were stored at minus 80 °C to avoid loss of quality according to practice guidelines of our research laboratory. Standard laboratory tests were performed according to guidelines of our hospital’s main laboratory. The serum concentrations of sST2 and IL-33 were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA)-kits (Human ST2/IL-33R DuoSet ELISA DYS23B-05 and Human IL-33
smoking history or pre-existing chronic disease except for coronary artery disease (CAD). Patients with sST2 levels ranging from 34.68–93.57 ng/ml were included in the final analysis. The cohort was divided into sST2 levels below or above the median for further analysis. The median sST2 level 24 h after ICU admission was 53.42 ng/ml (IQR 20.53–106.78 ng/ml). There were no significant differences in age, sex, body mass index, or sequential organ failure assessment (SOFA) score between independent groups. A Chi-square test was used to calculate univariate differences between groups. First, we divided the cohort into two sub-groups: patients below and patients above the median sST2 concentration of this cohort. The primary outcome was a composite endpoint after 6 months (death or CPC > 2); the secondary endpoint death after 30 days. Also, we stratified the cohort by sST2-level quartiles to investigate a graded association of sST2 level and prognosis. In addition, the associations of sST2 as a continuous variable and as a binary variable (above and below the median) were evaluated using logistic regression. Also, an optimal cut-off was calculated by means of the Youden index. Receiver operating curve (ROC) analysis was performed, and the area under the curve (AUC) was calculated. We created a univariable model as well as a multivariable model in which confounding factors (age, sex, and sequential organ failure assessment (SOFA) score) were included and calculated odds ratios (OR) as well as adjusted odds ratios (aOR) with their respective 95% confidence intervals (95% CI). The selection of confounding factors was based on our clinical experience as well as previous research. To investigate the association of being in the high-ST2 group and the secondary outcome, a univariate Cox proportional hazard model was used and hazard ratios (HR) were calculated. The survival curve was plotted using the Kaplan Meier curve. All tests were two-sided and a p-value < 0.05 was considered significant. We used Stata 16.1 (Stata Statistical Software: Release 16. StataCorp LLC, College Station, Texas, United States of America) for all statistical calculations.

 Ethics approval and consent to participate. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice and approved by the local ethics committee (415-E/2408/8-2018).

Results
A total of 106 patients were included in the final analysis. The cohort was divided into sST2 levels below or above the median for further analysis. The median sST2 level 24 h after ICU admission was 53.42 ng/ml (IQR 34.68–93.57 ng/ml) for the entire cohort. There were no significant differences in age, sex, body mass index, smoking history or pre-existing chronic disease except for coronary artery disease (CAD). Patients with sST2 levels below the median were more likely to have a history of CAD (24.5% vs. 9.4%, p = 0.038). Furthermore, no significant correlation could be shown for ejection fraction determined by transthoracic echocardiography. In Table 1 a detailed overview of general patient characteristics is provided. Supplementary Table 1 (Supplement 1) shows the results within quartiles of sST2 levels.

Regarding CPR-specific findings there was no difference between the two groups in the proportion of out-of-hospital cardiac arrests (OHCA) and in-hospital cardiac arrests (IHCA) (84.9% each, p = 1.000). No data were collected on first medical contact (paramedic vs. physician-based emergency medical service; EMS), yet all patients with OHCA were eventually admitted to our institution by physician-based EMS vehicles. Emergency response teams for IHCA were also led by physicians. Significantly more patients in the lower sST2 group received bystander CPR (49.0% vs. 28.3%, p = 0.040) whereas more patients in the higher sST2 group received CPR during transport (13.2% vs. 3.8%, p = 0.040). No relevant difference was found for initial rhythm, direct admission to the ICU or percutaneous coronary intervention (PCI). More patients with sST2 levels above the median received prehospital systemic lysis, which also did not reach statistical significance (11.4% vs. 5.2%, p = 0.296). Regarding post resuscitation care, patients in the group with higher sST2 levels more often received mechanical ventilation (100% vs. 88.7%, p = 0.012), targeted temperature management (83% vs. 54.7%, p = 0.002), continuous veno-venous hemodiafiltration (18.9% vs. 0%, p = 0.001) and antimicrobial chemotherapy (100% vs. 84.9%, p = 0.001), while no statistically significant difference but a trend towards more red cell blood transfusions was shown in the higher sST2-group (15.1% vs. 9.4%, p = 0.374). Table 2 provides a detailed overview of the characteristics associated with CPR- and post-resuscitation care. Supplementary Table 2 (Supplement 1) shows the results within quartiles of sST2 levels.

Standard laboratory values showed a significant difference in initial arterial pH- and lactate-values after ICU admission (high-sST2: median pH 7.131, median lactate 5.74 mmol/l vs. low-sST2: median pH 7.257, median lactate 3.58 mmol/l; p = 0.003 each). In addition, patients with higher initial sST2-levels had higher initial leukocyte counts (15.6 G/l vs. 12.6 G/l, p = 0.002). No relevant differences were observed in initial hemoglobin, platelet-count, C-reactive protein (CRP), serum creatinine, low-density lipoprotein (LDL) or HbA1c. A detailed list of all obtained laboratory values is provided in Table 3. Supplementary Table 3 (Supplement 1) shows the results within quartiles of sST2 levels.
Table 1. General patient characteristics. BMI body mass index, CAD coronary artery disease, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, IQR interquartile range, no. number, OSA obstructive sleep apnea, yrs. years. Ranges of percentage for left ventricular ejection fraction: (1) “normal”: males 52–72%, females 54–74%; (2) “mildly abnormal”: males 41–51%, females 41–53%; (3) “moderately abnormal”: both sexes 30–40%; (4) “severely abnormal”: both sexes < 30%.

| Characteristic                              | sST2 ≤ 53.42 ng/ml (n = 53) | sST2 > 53.42 ng/ml (n = 53) | p-value |
|---------------------------------------------|-----------------------------|-----------------------------|---------|
| Age (yrs.)—median (IQR)                     | 65 (57–74)                  | 64 (53–72)                  | 0.444   |
| Male sex—no. (%)                            | 38 (71.7)                   | 38 (71.7)                   | 1.000   |
| BMI (kg/m²)—median (IQR)                    | 25.6 (24.6–28.2)            | 26.2 (24.5–29.1)            | 0.675   |
| Arterial hypertension—no. (%)               | 37 (69.8)                   | 34 (64.2)                   | 0.708   |
| Hyperlipidemia—no. (%)                      | 33 (62.3)                   | 24 (45.3)                   | 0.076   |
| Diabetes mellitus—no. (%)                   | 7 (13.2)                    | 12 (22.6)                   | 0.170   |
| Smoking history—no. (%)                     | 24 (45.3)                   | 26 (49.0)                   | 0.657   |
| COPD—no. (%)                                | 7 (13.2)                    | 6 (11.4)                    | 0.767   |
| OSA—no. (%)                                 | 5 (9.4)                     | 2 (3.8)                     | 0.241   |
| CKD—no. (%)                                 | 11 (20.8)                   | 9 (17.0)                    | 0.653   |
| History of CAD—no. (%)                      | 13 (24.5)                   | 5 (9.4)                     | 0.038   |
| History of cardiac surgery—no. (%)          | 5 (9.4)                     | 3 (5.7)                     | 0.594   |
| Ejection fraction after admission—no. (%)   | -                           | -                           | 0.429   |
| Normal (1)                                  | 9 (17.0)                    | 8 (15.1)                    | -       |
| Mildly abnormal (2)                         | 9 (17.0)                    | 16 (30.2)                   | -       |
| Moderately abnormal (3)                     | 20 (37.7)                   | 15 (28.3)                   | -       |
| Severely abnormal (4)                       | 15 (28.3)                   | 14 (26.4)                   | -       |

Table 2. Patient characteristics regarding CPR and post-resuscitation care. CPR cardiopulmonary resuscitation, CVVHDF continuous veno-venous hemodiafiltration, ER emergency room, ICU intensive care unit, IQR interquartile range, OHCA out of hospital cardiac arrest, PCI percutaneous coronary intervention, PEA pulseless electrical activity, SOFA severity of organ failure assessment, TTM targeted temperature management.
Elevated sST2-levels 24 h after ICU admission were associated with a higher risk of the combined endpoint (death or CPC > 2) at 6 months (OR 1.011, 95% CI 1.004–1.019, p = 0.004). The optimal cut-off value for serum sST2 was 46.15 ng/ml (sensitivity 81%, specificity 53%, AUC 0.69). The corresponding ROC (receiver operating characteristic) curve is shown in Fig. 2a. There were no survivors with poor neurological outcome (CPC > 2) at 6 months. The association was significant for the secondary endpoint of death after 30 days (OR 1.011, 95% CI 1.004–1.02, p = 0.004). SST2-levels > 53.42 ng/ml were associated with higher odds for the primary endpoint (21% vs. 49%, OR 3.59, 95% CI 1.52–8.45, p = 0.003). SST2 levels above the median were also associated with higher risk of death at 30 days (OR 3.75, 95% CI 1.52–9.21; see Fig. 3a). By dividing the cohort into four groups (stratified by quartiles), a graded association of sST2 and the primary endpoint was shown (see Fig. 3b). In the multivariable model, the association of both sST2 as a continuous variable (aOR 1.09 95% CI 1.001–1.018, p = 0.004) as well as sST2 above the median (aOR 2.95 95% CI 1.52–8.45, p = 0.003) with the primary outcome remained after adjustment for potential confounders. Neither IL-33 levels (p = 0.35) nor IL-33/sST2 ratio (p = 0.64) 24 h after admission were associated with the primary outcome.

**Discussion**

In our observational prospective study of 106 consecutive patients after cardiopulmonary resuscitation, serum sST2-levels 24 h after hospital admission were associated with an increased risk of death at 30 days and 6 months.

In general, CA results not only in circulatory arrest, but also in microcirculatory shock with far-reaching metabolic, immunologic and coagulatory consequences. After return of spontaneous circulation a generalized inflammatory reaction occurs, better known as Post-cardiac arrest syndrome (PCAS). PCAS is primarily caused by four main players, namely the cause of arrest and possible sustained sequelae, full-body ischemia and reperfusion, as well as neurological and myocardial dysfunction. Thus, metabolically active organs are

| Characteristic | sST2 ≤ 53.42 ng/ml (n = 53) | sST2 > 53.42 ng/ml (n = 53) | p-value |
|----------------|-----------------------------|-----------------------------|---------|
| Initial pH overall—median (IQR) | 7.257 (7.163–7.329) | 7.151 (7.023–7.276) | 0.003 |
| Initial lactate overall (mmol/l)—median (IQR) | 3.58 (2.03–5.85) | 5.74 (3.12–9.26) | 0.003 |
| Hemoglobin (g/dl)—median (IQR) | 13.9 (12.9–14.6) | 13.8 (12.5–15.0) | 0.827 |
| Leucocyte count (G/l)—median (IQR) | 12.6 (10.3–15.4) | 15.6 (12.9–20.2) | 0.002 |
| Platelet count (G/l)—median (IQR) | 236 (203–277) | 230 (189–311) | 0.778 |
| CRP (mg/dl)—median (IQR) | 0.3 (0.2–0.8) | 0.5 (0.2–1.5) | 0.392 |
| Serum creatinine (mg/dl)—median (IQR) | 1.19 (1.02–1.37) | 1.28 (1.15–1.40) | 0.099 |
| LDL (mg/dl)—median (IQR) | 83 (54–111) | 65 (44–97) | 0.132 |
| HbA1c (%)—median (IQR) | 5.5 (5.3–5.7) | 5.5 (5.3–5.9) | 0.645 |

Table 3. Initial laboratory values. CRP C-reactive protein, IQR interquartile range, LDL low-density lipoprotein.
particularly affected. In addition to cardiovascular and neural stress, coagulation pathways and the cortisol-stress axis are also involved. Since both the origin of cardiac arrest and the exact onset of ischemia and reperfusion vary, it can be assumed that the subsequent defense response also varies in its strength and expression. A better understanding of the inflammatory pathways involved at the cellular level could facilitate clinical management and improve long-term outcome. Because circulatory arrest in CA affects all organ systems and the integrity of different vital organs is necessary for functionally intact survival, it is difficult to find a general biomarker for outcome prediction after CPR. After successful resuscitation, functional neurologic outcome is ultimately relevant, which is why resuscitation guidelines specifically mention biomarkers that may indicate neurological

Figure 3. (a) Kaplan–Meier plot for patients with sST2-levels below (red line) and above the median (blue line; median sST2-level 24 h after admission: 53.42 ng/ml). (b) Kaplan–Meier plot for patients stratified by sST2-level quartiles (blue line: quartile 1, sST2 < 34.68 ng/ml; red line: quartile 2, sST2 ≥ 34.68 ng/ml and < 53.42 ng/ml; green line: quartile 3, sST2 ≥ 53.42 ng/ml and < 93.57 ng/ml; yellow line: quartile 4, sST2 ≥ 93.57 ng/ml).
ST2 was originally thought to be primarily relevant in inflammatory diseases, but its role as an indicator of myocardial stress and inflammation is now recognized. Its active transmembrane isoform, ST2L, is believed to participate in the MyD88/NF-κB-pathway. This pathway is essential regarding innate immunity activation via pathogen associated molecular pattern recognition. Furthermore, it plays a role in regulation of T-helper cells type 2, regulatory T-cells, mastocytes and cells of the innate lymphoid system. ST2L and IL-33 appear to have cardioprotective effects, whereas sST2 serves as a decoy-receptor for IL-33 (and therefore attenuates protective properties of ST2/IL-33) and was previously associated with worse outcomes. Currently, sST2 is recognized as a relevant prognostic marker especially for patients with various cardiovascular diseases, such as ischemic heart disease and heart failure. However, it is not a cardio-specific parameter because it is not only produced in cardiomyocytes but also in other organs such as lung and kidney.

With regard to general patient characteristics, no significant differences were observed in our patient cohort with the exception of previously known CAD. Outcome analyses for sST2 in CAD have been performed in the past and higher baseline concentrations were associated with a risk of major adverse cardiac events in a recent meta-analysis of 17,432 individuals. Nevertheless, this finding must be interpreted with caution, since some patients in our cohort were certainly overestimated based on their medical records (CAD present, but clinically insignificant) whereas other patients were underdiagnosed, because not all patients received coronary angiography after CPR. Another interesting finding of our study was that no correlation was found with ejection fraction obtained by echocardiography. Although all patients were examined by experienced physicians with sufficient training in echocardiography, not all measurements were performed in a standardized manner, as for example Simpson’s method. The possibility of reversible myocardial dysfunction must also be considered. An interesting approach would be echocardiographic monitoring 72 h after CPR, as myocardial dysfunction is often transient and perhaps other sampling times would be necessary to reliably rule out an association between IL-33 levels and ejection fraction, as ejection fraction in contrast to diastolic function is known to be a weak outcome predictor after CPR. Unfortunately, diastolic function was not recorded in our database.

Regarding CPR-specific findings, significantly more patients in the high-sST2 group received bystander CPR in our study. We do not have information on the quality (laypersons vs. professionals), downtime and duration of resuscitative measures, but this finding indicates the prognostic value of early CPR and witnessed arrest. In the study by Ristagno et al., no correlation with bystander CPR was shown for sST2 levels 0 h and 48 h after admission, although patients with shockable rhythms had lower sST2-levels than patients with non-shockable rhythms. We could not fully reproduce this finding, although in our cohort, patients with higher sST2 levels (24 h after admission) were more likely to have pulseless electrical activity (PEA) as their initial rhythm. In a larger number of patients, this finding might have become statistically significant. In our study, patients with sST2 values above the median were also more likely to receive invasive measures like mechanical ventilation, antibiotics and hemodiafiltration and a higher rate of blood transfusions was observed, although this did not reach statistical significance. Regarding targeted temperature management (TTM), patients with higher sST2-levels received TTM more frequently. This is consistent with the results of Ristagno et al. 48 h after ROSC. Bro-Jeppesen et al. found that concentrations of inflammatory cytokines (inter alia IL-1β) were associated with PCAS but no alteration of the inflammatory response by TTM was shown. IL-1β-levels, which like ST2 belong to the IL-1 family, have been shown to correlate positively with sST2 in patients with acute decompensated heart failure. However, no specific analysis on sST2-levels was carried out in the Bro-Jeppesen study. Thus, clinically sicker patients (as reflected by the significantly higher SOFA-scores) most likely received TTM to a greater extent in our study. The decision to initiate TTM was made by the attending physician.

Regarding the laboratory values obtained, patients in the high sST2 group had both lower arterial pH- and higher lactate values after hospital admission. This is an expected finding, since both values have been associated with survival after CPR. Also, higher initial leucocyte counts (WBC) were found in the high sST2-group. Different observations have been made for WBC-count and sST2 in the past, as both positive and negative correlations with outcome have been observed in different diseases. A more detailed evaluation including manual differential blood counts might be more informative, as the ST2-/IL-33 axis has a variety of interactions with different leucocyte subpopulations. Interestingly, we did not find any relevant correlation with C-reactive protein (CRP) values, which we observed in a previous study in patients after transcatheter aortic valve replacement (TAVR). One possible explanation could be the timing of blood sampling, as Ristagno et al. demonstrated an association between higher sST2-, PTX3- and CRP-values 48 h after admission and poor outcome. For future studies, serial blood sampling after admission would be useful as the release kinetics of sST2 after CA is currently unknown.

No correlation was found for IL-33 and our study endpoints either. Different release kinetics could be a possible explanation for this finding. It is also consistent with the results of Zhuang et al., who observed increased IL-17- and IL-23- but not IL-33-levels in patients with poor outcome after PCAS. In our own experience, IL-33 is not a strong direct predictor of outcome in cardiovascular disease. Nevertheless, a study with more participants and perhaps other sampling times would be necessary to reliably rule out an association between IL-33-levels and prognosis after CPR.

**Limitations**

One limitation is the single-center character of this study, so it was not possible to include a larger number of patients. Information on downtime, quality of CPR, time to ROSC and duration of resuscitative measures is also lacking. Furthermore, conventional neuroprognostication markers such as NSE and S-100B protein, or novel markers like glial fibrillary acidic protein, serum tau protein and neurofilament light were not obtained by default.
in every patient. Because there was a relatively large group with a good neurological outcome in this patient population, the informative value of sST2 as a neuroprognostication marker is relatively low.

Conclusion
In our prospective study of 106 patients after cardiopulmonary resuscitation, we found a positive correlation between serum sST2-levels and mortality at 30 days and 6 months after cardiac arrest. This study should contribute to current research on the inflammatory response after cardiac arrest and could serve as a basis for future studies.

Data availability
All data relevant for this study will be given by the authors upon specific request without restriction.

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**Author contributions**

V.P. carried out the laboratory analyses. B.W. participated in the design of the study and performed the statistical analysis. R.R., C.S., P.S., R.K. and M.L. analyzed the data and wrote the first draft of the manuscript. K.K. revised the language of the manuscript and gave content guidance. I.P., T.K.F., E.P., G.G., R.P. and U.C.H. gave guidance and improved the paper.

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