Right ventricular outflow tract Doppler flow analysis and pulmonary arterial coupling by transthoracic echocardiography in sepsis. A retrospective exploratory study

Emma Maria Bowcock (emma.bowcock@hotmail.com)
Nepean Hospital
Benjamin Gerhardy
Nepean Hospital
Stephen Huang
Nepean Hospital
Sam Orde
Nepean Hospital

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Abstract

Introduction: Right ventricular (RV) and pulmonary vascular dysfunction are common in sepsis and are associated with worse outcomes. RV performance is frequently assessed in isolation, yet its close relationship to afterload means combined evaluation with analysis of right ventricular outflow tract (RVOT) Doppler and RV-pulmonary arterial (RV-PA) coupling may be more informative. Data on feasibility, utility and prognostic significance of these parameters in sepsis is lacking and was explored in this study.

Methods: Retrospective study over a three-year period of one-hundred and thirteen patients admitted to ICU with sepsis who had a transthoracic echocardiography with RVOT pulse wave Doppler (PWD). RVOT Doppler flow and RV-PA coupling was evaluated alongside other measurements of RV systolic function and pulmonary pressures. RVOT Doppler analysis included assessment of pulmonary artery acceleration time (PAAT) and presence of notching. RV-PA coupling was assessed using tricuspid annular planar systolic excursion/ pulmonary artery systolic pressure (TAPSE/PASP) ratio. Discriminatory performance of PAAT and RV-PA coupling for ICU and hospital mortality were assessed using receiver operating characteristic (ROC) curves.

Results: PAAT was measurable in 106 (94%) patients and TAPSE/PASP was measurable in 77 (73%). 69% had a PAAT of less than 100msec suggesting raised pulmonary vascular resistance (PVR). PAAT was significantly shorter in those with RV-PA uncoupling (p=0.006). There was a trend towards shorter PAAT with increasing RV dysfunction (RVD) severity. Tricuspid regurgitant maximum velocity (TRVmax) was unable to be assessed in 24 (23%) patients where measurement of PAAT was possible. TAPSE/PASP <0.4mm/mmHg and PAAT corrected for heart rate (PAATc) < 76msec predicted hospital mortality with area under ROC curve of 0.7 and 0.8 respectively. Patients with a PAATc of <76mec had increased ICU and hospital mortality: OR 13.2 [CI 1.6-108] p=0.005 and OR 14 (3.2-65) p<0.001, respectively. TAPSE/PASP <0.4mm/Hg disclosed an increased hospital mortality (OR 4.4 [CI 1.3-15], p=0.02).

Conclusion: Raised PVR and RV-PA uncoupling occur frequently in sepsis. Non-invasive assessment is feasible, and evaluation of these parameters could have prognostic utility. Their role in assisting improved definitions of RV dysfunction as well as their therapeutic significance requires further investigation in prospective studies.

Key Messages

- Increased pulmonary vascular resistance and RA-PA coupling are common in those with sepsis and measurement with TTE is feasible.
- Shortened PAAT and RV-PA uncoupling may have prognostic utility in sepsis and could aid in improving definitions of right ventricular dysfunction.
- The therapeutic role of these parameters in sepsis is unknown and further prospective studies are needed.

Background

Right ventricular dysfunction (RVD) is common in sepsis and seems to be associated with increased mortality (1,2). Direct myocardial injury plus increased afterload from increased pulmonary vascular resistance (PVR) are likely important factors in sepsis related RVD (3–5). RVD is a heterogenous, ill-defined syndrome and better definitions of 'RVD phenotypes' are needed (6,7). RV performance is frequently assessed in isolation yet is closely related to afterload; combined evaluation with the assessment of the pulmonary circulation may be more informative (8,9). Non-invasive assessment of 'RV – Pulmonary arterial (PA) coupling' using surrogates such as TAPSE/ pulmonary artery systolic pressure (TAPSE/PASP) have shown prognostic utility in recent studies (10,11). Data on feasibility, utility and prognostic significance in sepsis is lacking, however. In a substantial proportion of critically ill patients PASP cannot be accurately measured from tricuspid regurgitant maximum velocity (TRVmax) (12). Evaluating the time the right ventricle takes to achieve peak ejection, e.g., pulmonary artery acceleration time (PAAT), has utility in identifying those with PH where PASP is not available(13,14). Evaluation of the right ventricular outflow tract (RVOT) Doppler flow and RV-PA coupling could provide rapid, non-invasive pulmonary haemodynamic information to improve our understanding of RV performance and identify modifiable factors.

The objective of this exploratory study was to generate hypothesis for future prospective study. We assessed the feasibility of RVOT Doppler waveform analysis and RV-PA coupling and explored these parameters in relation to RV function, pulmonary pressures and mortality.

Methods

Single centre, retrospective analysis of RVOT systolic flow profiles recorded by pulsed-wave Doppler (PWD) in all patients (> 18years) admitted with a primary diagnosis of sepsis who had a transthoracic echocardiogram (TTE) performed in ICU. Of 455 patients who were admitted to our unit with sepsis during July 2018 – April 2021, 131 patients had a full transthoracic echo (TTE) study by trained sonographers that included PWD of the RVOT. Of those, 106 were sufficient for analysis. Those with congenital heart disease or known intracardiac shunts were excluded.

Echo and clinical data were obtained from local intensive care echocardiography and clinical system databases respectively. Measurement of PAAT, RVOT ejection time (ET) and RVOT velocity time integral (VTI) was performed using an offline software analysis package by intensive care specialists with advanced echo qualification (EB, SO) (Fig. 1).

An average measurement of PAAT was taken from 3 (or 5 if in atrial fibrillation) consecutive RVOT Doppler profiles. PAAT corrected for heart rate (PAATc) was calculated using the formula PAAT x 75/HR (15). Blinded interobserver variability for PAAT analysis was assessed by an echo trained specialist (BG) on a random 20% subgroup.

RVOT Doppler profiles were categorised as No notch (NN) and Notched (N) (Fig. 1). The notch position was defined by time-to-notch ratio, calculated as the time between the onset of the ejection to the notch to the ejection time. If this ratio was less than 0.66 (i.e., notch occurring within first 2/3rds of flow) and subjective assessment agreed the notch was characterised as mid systolic notching (MSN), others were characterised at late systolic notching (LSN)(16).

TAPSE/PASP was used as non-invasive measure of RV- PA coupling. A ratio of < 0.31 mm/mm Hg was used as the cut off to define RV-PA uncoupling based on previously published data(17).

PASP was calculated by the Bernoulli equation using tricuspid regurgitant maximum velocity squared ($4xTRVmax^2$) + RAP (estimated to be 10mmHg) (18). Patients were divided into subgroups of severity: mild (35-49mmHg), moderate (50- 70mmHg) and severe (> 70mmHg). TRVmax was also used to detect PH as suggested in recent guidelines (13). Values of $\geq$ 2.8m/s and > 3.4m/s were used to represent possible and probable PH respectively. This method eliminated the difficult issue of estimating RAP in critically ill patients.

Three definitions of RVD were used: Reduced systolic function by subjective assessment, decreased TAPSE of < 17mm and RV dilation. Subjectively reduced systolic function was further categorised as mild, moderate or severe. RV dilatation was categorised as mild if the RV was greater than two thirds the size of the LV but smaller than the LV, moderate if the RV was the same size as the LV and severe if the RV was larger than the LV and apex forming.

Raised left atrial pressure (LAP) due to left heart systolic or diastolic dysfunction causing pulmonary vascular remodelling can lead to raised PVR and may shorten PAAT. A simplified method proposed in a previous study (19) was used to infer raised LAP in this study: LV ejection fraction less than 45% with a mitral PWD inflow E/A velocity > 1.5.

Ethics approval was gained through local blue mountains health district research governance office. Consent was not required due to the retrospective nature of the study and hence a waiver of consent was sought.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD); skewed distributed continuous data were expressed as median and interquartile range [IQR]; categorical variables were expressed as counts and percentages. For comparisons between continuous variables a two-sided independent t test or Mann Whitney U test was used for normally distributed and non-normally distributed variables respectively. For comparison between categorical variables, contingency tables with X^2 test, or Fisher's exact test if less than 5, were used. Analysis of variance (ANOVA) testing was used to compare across more than 2 groups and post-hoc pairwise comparison was made using TukeyHSD. Normality was tested using Shapiro-Wilk test. Linear regression analyses and partial correlation test by Pearson's method were used to assess univariate relations. Discriminatory performance is assessed by odds ratio,

95% confidence interval and area under the receiver operating characteristic curve. Interobserver variability for PAAT was assessed using Bland-Altman analysis for 20% of random individuals from the cohort. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using Jamovi software 2022, version 2.3.

Results

Patient characteristics

The mean age was 65 [13] years with 58% male. 91% were alive at ICU discharge (n = 96) and 83% alive at hospital discharge (n = 88). Median length of ICU was 3.9(4) days with no significant difference between ICU survivors and non-survivors. Median hospital length of stay was 14(25) days in hospital survivors and 6.8 (13) days in those who died in hospital (p = 0.01). Nine (8%) patients had sepsis of urinary tract origin. Thirty-three patients (31%) were mechanically ventilated, 85 patients received inotropic support (80%) and 13 (12%) received renal replacement therapy during their admission. Twelve (11%) patients were in atrial fibrillation at the time of TTE. APACHE3 score was significantly higher in ICU non-survivors. There was no significant difference in chronic comorbidities between ICU survivors and non survivors, except for immunosuppressed patients where ICU mortality was higher. Admission arterial partial pressure of oxygen/fraction of inspired oxygen ratio, partial pressure of carbon dioxide and lactate was not significantly different between ICU survivors and non survivors. The highest bilirubin and creatinine level during admission were not significantly different in survivors to non survivors (Table 1).

Table 1
baseline characteristics between survivors and non survivors. Data presented as absolute value and (%), mean ± standard deviation or median (interquartile range).

Patient characteristics	ICU Survivors (n = 96)	ICU Non-Survivors (n = 10)	P value
Age	65 ± 13	65 ± 15	0.89
Male	55 (57%)	6 (60%)	1
Weight (Kg)	94 ± 35	79 ± 33	0.25
APACHE 3	**72 ± 23**	**101 ± 26**	**< 0.001**
ICU length of stay (days)	4.1 (4)	3.1 (4.6)	0.80
Invasive ventilation	27 (27%)	6 (60%)	0.06
Renal replacement therapy	**9 (9%)**	**4 (40%)**	**0.01**
Inotropes	75 (78%)	10 (100%)	0.09
HR bpm during TTE	**84 (23)**	**115 (11)**	**< 0.001**
Atrial fibrillation during TTE	11 (11%)	1 (10%)	0.89
Chronic cardiovascular disease	4 (4%)	0	1
Chronic respiratory disease	17 (18%)	2 (20%)	1
Chronic renal disease	5 (5%)	0	1
Cirrhosis	3 (3%)	1 (10%)	0.33
Immunosuppressed	**13 (14%)**	**4 (40%)**	**0.05**
Lactate on admission, mmol/L	1.6 (2.4) (n = 85)	2.3 (2.5) (n = 9)	0.09
pH on admission	7.36 ± 0.09 (n = 83)	7.33 ± 0.09 (n = 9)	0.34
P/F ratio on admission	235 (175) (n = 83)	227 (221) (n = 9)	0.99
PaC02 on admission	38 (11) (n = 83)	41 (17) (n = 9)	0.56
Bilirubin	11 (15) (n = 76)	17 (20) (n = 9)	0.26
Creatinine	134 (156) (n = 94)	122 (134) (n = 10)	0.63

Feasibility and interobserver variability

RVOT waveform analysis was possible in 106 (80%) of TTE studies with RVOT PWD traces. TRVmax was unavailable in 24 (23%) patients where RVOT Doppler flow measurement of PAAT was available suggesting PAAT measurement may be more feasible in our patient group. Time to notch ratio was able to be determined in all patients with notching of the RVOT waveform. RV-PA coupling using TAPSE/PASP

ratio was measurable in 77 (73%) of patients. Bland- Altman analysis showed acceptable agreement in PAAT measurement with a mean difference of 4msec (upper and lower limits of agreement − 3.9–12msec).

RVOT Doppler analysis

The mean PAAT was 91 ± 20msec. Seventy-three patients (69%) had a PAAT of ≤ 100msec, which is often used as a cut off to suggest raised PVR. A notched RVOT Doppler profile was detectable in 15 patients (14%). PAAT was significantly shorter in those with notching (76 ± 14 v. 93 ± 20, p = 0.002). Fourteen (93%) of those with notched profiles had a PAAT of ≤ 100msec. Eleven patients (73%) had mid systolic notching (MSN). Other values of RVOT Doppler analysis are shown in Table 2 and 4.

Table 2
Association of RVD by subjective assessment and RVOT analysis. Mean ± standard deviation. RV function group 1 = normal, 2 = mild, 3 = moderate, 4 = severe dysfunction

RVD by subjective assessment severity groups	N	PAAT (msec)	*RVOT VTI(cm)*	*RVOT ET (msec)*	*Mid systolic DT (msec)*
Normal	79	92 ± 21	**15 ± 4**	277 ± 49	164 ± 45
Mild	16	89 ± 18	**13 ± 3**	264 ± 57	143 ± 52
Moderate	9	86 ± 13	**10 ± 2**	280 ± 53	124 ± 49
Severe	3	63 ± 11	**6 ± 1**	188 ± 91	124 ± 58
p value		0.07	**< 0.001**	0.4	0.2

Table 3
Echocardiographic findings in ICU survivors and non survivors

Echocardiographic findings	ICU Survivors (n = 96)	ICU non-Survivors (n = 10)	P value
PAAT (ms)	92 ± 21	79 ± 14	0.06
PAATc (ms)	**80 ± 41**	**51 ± 23**	**0.003**
RVOT ET (ms)	**278 ± 50**	**225 ± 61**	**0.002**
RVOT VTI (cm)	14 ± 4	13 ± 2	0.26
Notching (%)	14 (15%)	1 (10%)	1
RV dysfunction -subjective	25 (26%)	3 (30%)	0.72
TAPSE (mm)	19 ± 6 (n = 91)	20 ± 4 (n = 9)	0.83
RV dilation	32 (33%)	4 (40%)	0.73
PASP (mmHg)	41 ± 12 (n = 75)	50 ± 13 (n = 7)	0.06
TRVmax (m/s)	2.7 ± 0.5 (n = 75)	3.1 ± 0.5 (n = 7)	0.06
TAPSE/PASP	0.49 ± 0.25 (n = 71)	0.35 ± 0.19 (n = 6)	0.23
TAPSE/PAAT	0.22 ± 0.1 (n = 91)	0.22 ± 0.1 (n = 10)	0.9
TAPSE/PAATc	**0.25 ± 0.1 (n = 91)**	**0.33 ± 0.2 (n = 10)**	**0.04**
PAAT/PASP	**2.5 ± 1 (n = 75)**	**1.6 ± 0.6 (n = 7)**	**0.04**
PAATc/PASP	**2.3 ± 1.2 (n = 75)**	**1 ± 0.4 (n = 7)**	**< 0.001**
LV ejection fraction (%)	**51 ± 13**	**61 ± 8**	**0.02**
E/e'	10 (3) (n = 92)	9 (3) (n = 9)	0.25
E/A	1.2 ± 0.6 (n = 70)	1.2 ± 0.5 (n = 7)	0.94
Lateral e' (cm/s)	9 ± 3 (n = 93)	11 ± 5 (n = 9)	0.29
Medial e' (cm/s)	8 ± 8 (n = 93)	8 ± 3 (n = 9)	0.98

Table 4
Cut off points for PAATc (msec), TAPSE/PASP (mm/mmHg) and PAATc/PASP (msec/mmHg) and corresponding sensitivity, specificity and area under curve (AUC).

Variable	*Cut off ICU mortality*	*Sensitivity*	*Specificity*	*AUC*
PAATc (msec)	*56*	*86%*	*60%*	*0.8*
TAPSE/PASP (mm/mmHg)	*0.4*	*72%*	*69%*	*0.7*
PAATc/PASP (msec/mmHg)	*1.1*	*91%*	*71%*	*0.9*
	Cuff off Hospital mortality	Sensitivity	Specificity	AUC
PAATc(msec)	*73*	*65%*	*83%*	*0.8*
TAPSE/PASP (mm/mmHg)	*0.4*	*72%*	*69%*	*0.7*
PAATc/PASP (msec/mmHg)	*1.5*	*74%*	*71%*	*0.8*

RV-PA coupling

RV-PA uncoupling defined by TAPSE/PASP ratio of < 0.31mm/mmHg was present in 15 patients (20%). PAAT was significantly more likely to be ≤ 100ms in those with RV-PA uncoupling ($p = 0.05$) as compared to other definitions of RVD. In those with RV-PA uncoupling, presence of notching was significantly more likely (*OR 7.6 [CI 1.9–30], p = 0.005)*. Those with RV-PA uncoupling had significantly more RV dilatation (OR 9.8, [CI 2.5–39], $p < 0.001$). RVD by subjective assessment was also more likely in those with RV-PA uncoupling (OR 14.3 [CI 3.8–54], $p < 0.001$).

A cut off TAPSE/PASP ratio of 0.4 mm/mmHg for ICU and hospital mortality was found in this study with an AUC of 0.7. This was used to explore the relationship with RV-PA uncoupling and PAAT. RV-PA uncoupling defined by TAPSE/PASP < 0.4 mm/mmHg was present in 25 (33%) of patients and disclosed a significantly shorter PAAT (82 ± 16 v 95 ± 21msec, $p = 0.006$) (Fig. 2). The correlation between TAPSE/PASP and PAAT was moderate but significant (r 0.4, $p < 0.001$).

Right ventricular dysfunction

RVD was present in 28(26%), 26 (26%), and 36 (34%) patients if subjective, TAPSE < 17mm and RV dilatation was used respectively. Analysis of variance between RV dysfunction severity subgroups by subjective assessment and RVOT Doppler analysis is shown in Table 2. As expected, RVOT VTI was significantly lower as RVD severity increased ($p < 0.001$). Post hoc pairwise comparison showed this was statistically significant across normal to moderate ($p = 0.006$), normal to severe ($p = 0.002$) and mild to severe ($p = 0.04$) severity subgroups. There was a trend towards shorter PAAT with increasing RVD severity by subjective assessment that was not statistically significant ($p = 0.08$) (Fig. 3). In those with RVD defined by TAPSE < 17mm there was no significant difference in PAAT (87 ± 20 v. 93 ± 21, $p = 0.24$).

There was no significant difference in PAAT in those with RV dilatation (92 ± 21 v. 90 ± 19, p = 0.75). Differences were not significant when PAAT was corrected for HR (PAATc).

As expected, the prevalence of subjective RVD (14%) and RV dilatation (16%) was increased in those with RV-PA uncoupling defined as a ratio of < 0.31mm/mmHg as compared to those without RV-PA uncoupling (P < 0.001 and p < 0.001 respectively).

A PAATc/PASP ratio of < 2 correlated with a PVR of > 3 wood units (WU) in previous validation studies(14). PAATc/PASP or PAAT/PASP < 2 was not associated with RVD by subjective assessment or TAPSE < 17mm (p = 0.2 and p = 0.1 respectively). RV dilatation was more likely in those with a PAAT/PASP < 2 (OR 2.6 [CI 1.0- 6.6] p = 0.04). Analysis of variance between subjective RVD severity groups revealed no difference in PAAT/PASP ratios (p = 0.8).

Pulmonary pressures

Pulmonary hypertension (PH), defined as PASP ≥ 35mmHg was present in 56 (68%). A TRVmax of ≥ 2.8m/s was present in 37 (45%) and a TRVmax of > 3.4 m/s was present in 10 (12%). A moderate but significant inverse correlation was found between PAAT or PAATc and 4xTRVmax^2 (r 0.31, p = 0.002 and r 0.34, p < 0.001 respectively). PASP was significantly higher in those with RVOT Doppler notching (51 ± 15 mmHg v. 40 ± 11 mmHg, p = 0.003).

Severity subgroups of PH were as follows: mild (35-49mmHg) in 37 (35%), moderate (50- 70mmHg) in 15 (14%) and severe (> 70mmHg) in 3 (2.8%). Analysis of variance between RVD subjective severity subgroups revealed no significant difference in PASP values (p = 0.4). There was no significant difference in TRVmax in those with RVD by subjective assessment (p = 0.4) or TAPSE < 17mms (p = 0.7). Analysis of variance between groups revealed no significant differences in TRVmax with increasing severity of RVD by subjective assessment (p = 0.3) or increasing severity of RV dilatation (p = 0.1).

There was a significantly shorter PAAT with increasing severity of PH by subgroup analysis of variance (p 0.03). Post hoc pairwise comparison revealed a significant difference between those with normal to mild (p = 0.003) and normal to severe PH (p = 0.05) (Fig. 3).

LV systolic and diastolic function

Left ventricular systolic function was decreased in 29 (27%) patients defined by an ejection fraction (EF) of < 50%. 11 (10%) had combined reduced LVEF and RVD by subjective assessment. PAAT was not significantly different in those with normal or reduced EF (86 ± 17 vs. 92 ± 21ms, p 0.2). E/A ratio was measurable in 77 (73%) patients. Of these, 5 (6.5%) had an LVEF < 45% and E/A > 1.5 suggesting raised LAP. There was no significant difference in PAAT in those with reduced LVEF < 45% and E/A < 1.5 (normal LAP) or > 1.5 (high LAP) (92 ± 26 v. 92 ± 20ms, p = 0.98). There was no difference in presence of RVD between those with normal and raised LAP (p = 0.90).

Mortality

Echocardiographic findings between ICU survivors and non survivors are shown in Table 4. PAAT and PAATc were both significantly shorter in those who died in hospital (Fig. 4). PAATc was significantly shorter in those that died in hospital; there was a trend towards shorter PAAT in those that died in ICU that was not statistically significant (Fig. 4). There was no difference in the presence of notching between survivors and non survivors.

Cut off values derived from ROC curves are shown for PAATc, PAAT/PASP and TAPSE/PASP in Fig. 5. The corresponding cut off values, sensitivity, specificity and area under curves are shown in Table 4.

The odds ratio for ICU and hospital mortality with dichotmoised groups of PAATc and RV-PA uncoupling are shown in Table 5. Using cut off values of < 53msec and < 76msec for PAATc derived from ROC curves, ICU and hospital mortality were significantly increased (Table 5). Considering surrogates of RV-PA coupling, a cut off value of TAPSE/PASP < 0.4 mm/mm Hg as a definition for RV-PA uncoupling disclosed a significant increase in hospital mortality (OR 4.4 [CI 1.3–15], p = 0.02). There was a trend toward increased ICU mortality with TAPSE/PASP < 0.4 mm/mm Hg that was not statistically significant (OR 4.8 CI 0.8–28, p = 0.08). RVD by subjective, TAPSE or RV dilatation definitions were not associated with increased ICU or hospital mortality. Neither TRVmax $\geq$ 2.8m/s of >3.4m/s were associated with increased ICU (OR 1.9 [0.4-9] p = 0.5 and 3.4 [0.6–20], p = 0.2, respectively) or hospital mortality (OR 1.4 [0.5-5], p = 0.6 and 2.4 [0.5–11] p = 0.4, respectively)

Table 5
Odds ratio for mortality in PAATc and RV-PA uncoupling dichotomised groups. Trend towards increased ICU mortality with RV-PA uncoupling by cut off values of < 0.31 and < 0.4 that was not statistically significant.

Groups	Odds ratio ICU mortality	Odds ratio hospital mortality
PAATc <53msec	**8.6 [2.1–35],p = 0.005**	**4.4 [CI 1.3–16] P = 0.02**
PAATc <76msec	**13.2 [CI 1.6–108] p = 0.005**	**14 (3.2–65) p < 0.001**
TAPSE/PASP < 0.31	4.9 (CI 0.9–27) p = 0.08	3.4 (0.9–12) p = 0.1
TAPSE/PASP < 0.4	4.7 (0.8–28) p = 0.08	**4.4 (1.3–15) p = 0.02**

LV ejection fraction (LVEF) was significantly higher in ICU non survivors (51 ± 13 v. 61 ± 8, p = 0.02), however no difference was found in LVEF in those that died in hospital (52 ± 12 v 56 ± 16,p = 0.2). Those with a higher HR during TTE had increased ICU and hospital mortality (115 (11) v. 84 (23), p < 0.001 and 109(27) v. 84(23), p = 0.03 respectively).

Discussion

In this single centre, observational cohort study of 106 ICU patients with sepsis we demonstrated that analysis of the RVOT Doppler waveform and RV-PA coupling is feasible and holds interesting clinical

hypotheses. Increased PVR and RV-PA uncoupling were present in a significant proportion of patients. There was a trend towards increased ICU and hospital mortality in those with non-invasive surrogates of increased PVR: PAATc and PAATc/PASP. This is in keeping with previous small studies that have demonstrated raised PVR is associated with increased mortality in sepsis (20,21). Vieillard Baron et al. have shown TAPSE does not discriminate RV failure in patients with sepsis(22). Zhang et al. found markers of RV systolic function fail to prognosticate in ARDS(23). RVD defined by reduced TAPSE or subjective assessment was not associated with increased mortality in our study and are supportive of these findings. Those with RV-PA uncoupling defined by TAPSE/PASP < 0.4mm/mmHg had a higher hospital mortality and were significantly more likely to have raised PVR. This is in keeping with studies in the non-critically ill (24). Our findings suggest increased PVR with RV-PA uncoupling is perhaps more prognostically significant than RVD assessed by TAPSE or subjective assessment in sepsis.

The incidence of RVD varied in this study depending on the definition used. This highlights issues that currently exist with heterogeneity and poorly defined diagnostic categories of RVD (25). A standardised assessment for RV studies as described by Huang et al. in the PRICES expert statement could help mitigate such issues in future prospective studies(26). Invasive measures of RV-PA uncoupling (pressure-volume loop-derived end-systolic elastance (Ees)/end-systolic to arterial elastances (Ea)) using right heart catheterisation (RHC) is considered gold standard. Solda et al. have shown that a TAPSE/PASP ratio of < 0.31mm/mmHg correlates with invasive Ees/Ea (17). TAPSE provides an estimate of RV contractility and PASP an estimate of RV afterload. When the RV fails to augment contractility with increased afterload RV dilation occurs via heterometric adaptation (27). Others have found cut off values of < 0.36 mm/mmHg to correlate with mortality and PVR in heart failure (28). A TAPSE/PASP < 0.635mm/mmHg was associated with increased mortality in COVID 19 ARDS(11). Lower Tricuspid annular systolic velocity/right ventricular systolic pressure (TASV/RVSP) ratios were associated with increased mortality in a large retrospective data set of 4259 patients in cardiac intensive care(10). Animal models have shown RV-PA uncoupling occurs as sepsis severity increases (29). Our study has shown RV-PA coupling is common in patients admitted to ICU with sepsis. A third of patients had a TAPSE/PASP cut off of < 0.4mm/mmHg that revealed an AUC of 0.7 for both ICU and hospital mortality. To our knowledge there are no prospective studies evaluating RV-PA coupling in sepsis.

RV-PA coupling may have a role in helping define RVD phenotypes and the therapeutic significance of RV-PA uncoupling in sepsis requires further investigation. It may be important to differentiate RVD subgroups into those with preserved and uncoupled RV-PA interaction as treatment strategies may vary. For example, in those with RV-PA uncoupling the use of pulmonary vasodilators could be of benefit to lower PVR and improve RV performance. Overall, the findings suggest that moving from an isolated RV assessment to evaluation that incorporates the inextricable linkage to the pulmonary vasculature could have greater prognostic utility. This hypothesis is of interest to inform future prospective study design.

Various cut off values of PAAT ranging from 90msec to 105msec to detect raised PVR and/or PH have been described in the non-critically ill (30). Tossavavinen et al. showed a PAAT less than 90msec had superior accuracy (83%) to other non-invasive measures in identifying patients with raised PVR of > 3 WU

when compared to the gold standard right heart catheterisation (RHC). In our study, PAATc values of < 73msec were significantly associated with increased ICU and hospital mortality. The PAATc/PASP ratio has correlated with PVR (r = − 0.67, p 0.001) in previous studies, and a cut off PAATc/ PASP of < 2 had a positive and negative predictive value of 83% and 79% respectively to predicting PVR > 3WU in this study(14). In our study, lower PAATc/PASP ratios were associated with increased ICU and hospital mortality. A cut off value of < 1.1 revealed an AUC of 0.9. Although challenging, further validation studies using TTE measured PAAT, PASP, TAPSE/PASP and RV function against invasively measured PVR, PASP and RV ejection fraction with fast response PA catheters could be useful to further inform use of these parameters in our cohort.

TRVmax to estimate pulmonary pressures was unavailable in 24 (23%) patients where RVOT Doppler flow measurement of PAAT was available. This is an important finding in our patient group as a significant proportion of patients with pulmonary vascular dysfunction can be missed if pulmonary pressures are relied upon in isolation (15,31). Yared et al.(32) found a strong inverse correlation (r-0.95) between TTE measured PAAT and 4x $TRVmax^2$ in the non-critically ill. In contrast, a weak-moderate inverse correlation was found in our study. These conflicting results may be accounted for by the vastly different patient populations studied. Critically ill patients have varying degrees of RVD, tricuspid regurgitation and often inadequate spectral Doppler traces, all of which may affect values of TRVmax for calculation of PASP. Further studies evaluating TTE PAAT measurement against TTE derived PASP taking into account the caveats mentioned could inform the lack of strong correlation in the critically ill.

In the presence of increased PVR, reflected waves propagate more rapidly, with less attenuation, arriving at the RVOT during systole and causing systolic notching (Fig. 1). Systolic notching can be categorised mid systolic (MSN) or late systolic notching (LSN). The presence of a pulmonary MSN is more likely to represent increased pulmonary vascular resistance and poor vascular compliance. Those with a MSN pattern have the most severe pulmonary vascular disease and worst RV function in some studies (16). Takathama et al. found signal notching, shortening of the mid-systolic deceleration time, and diminution of the late systolic flow velocity confer a higher mortality risk in those with PH(33). In our study, 14% of patients had evidence of RVOT flow notching, and this was mostly MSN, suggesting significantly raised PVR. Interestingly, in those with severe RVD by subjective assessment did not have notching, whereas those with RV-PA uncoupling were significantly more likely. Further prospective study of RVOT notching patterns in those with preserved RV-PA coupling versus RV-PA uncoupling in sepsis would be of interest, particularly with dedicated imaging optimisation for assessment of the RVOT Doppler profile.

Left heart dysfunction is common in sepsis(34) and those with PH secondary to left heart failure (isolated postcapillary PH) have normal PVR (below 3 WU) and raised LAP. It is unknown what haemodynamic subgroups of PH are more common in sepsis. We evaluated for raised LAP using a simplified approach previously reported by Brault et al. (19), where an E/A ratio > 1.5 in those with reduced EF of $\leq 45\%$ predicted raised LAP when correlated with pulmonary artery occlusion pressure. In those with ‘raised LAP’ the PAAT was not significantly shorter. This is hypothesis generating to suggest raised PVR in sepsis could have a significant pre-capillary component.

Limitations

The limitations of this present study are inherent to its retrospective, single centre design. As such, conclusions drawn can be hypothesis generating only. ICU and hospital mortality rate was low limiting inference about correlation of echocardiographic parameters with mortality. Only those who had a TTE were included introducing possible selection bias. The type and dose of haemodynamic support as well as ventilation status at the time of TTE was not known limiting interpretation and generalisability of the findings. The ventilator settings and gas exchange, in particular driving pressure, plateau pressure, PEEP, partial pressure of C02 and Pa02/Fi02 ratio were not known at the time of RVOT assessment and may have influenced values obtained. In addition, it was not known if the RVOT PWD was taken during expiration or inspiration. Though it is suggested than taking an average of 3–4 consecutive cycles is a reasonable method to mitigate the effects of respiratory variation(12) The evaluation of RVD by subjective assessment introduces bias, though three different definitions of RVD were used to mitigate this. Chronic co-morbidities of patients were unknown including pre-existing PH, RVD, diastolic dysfunction, valvular disease and these factors are likely to impact measurements. The lack of other important echocardiographic markers of such as RV end diastolic/LV end diastolic area ratio, eccentricity index, RV strain, RV fractional area change, RV systolic velocity (s'), RVOT area, TR severity, IVC size and collapsibility as well as hepatic and portal venous flow, could have added further important information about RV performance. In addition, and perhaps most importantly, accurate central venous pressure (CVP) measurement was unavailable; CVP is crucial in this group of patients given its integral relationship to defining RV failure (25). All of these parameters would be important to include in subsequent prospective study design.

Conclusions

Increased pulmonary vascular resistance and RV-PA uncoupling occur commonly in the critically ill with sepsis. Much remains unknown about their prognostic and therapeutic significance. Classifying 'RVD phenotypes' to enable more precise definitions is a key priority. Evaluation of the 'RV-pulmonary circuit interaction' using RVOT Doppler waveform analysis and RV-PA coupling surrogates could provide some answers and further investigation is warranted.

Abbreviations

RVD: right ventricular dysfunction; RVOT: right ventricular outflow tract; PVR: pulmonary vascular resistance; PAAT: pulmonary artery acceleration time; PAATc: pulmonary artery acceleration time corrected for heart rate; VTI: velocity time integral; ET: ejection time; RV-PA: right ventricular- pulmonary artery; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular planar systolic excursion; TRVmax; tricuspid regurgitation maximum velocity; TTE: transthoracic echocardiography; PWD:pulsed wave Doppler; MSN: mid systolic notching

Declarations

Ethical Approval and Consent to participate

The study protocol was approved by the Blue Mountains Health District research governance office. Consent to participate was waived for this article.

Consent for publication

Not applicable

Availability of data and materials

The data and material used in this article belong to the corresponding author and can be accessed with permission

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

EB and SO conceived the article and participated in the design and coordination. BG assisted with design, conducted interobserver measurements and reviewed the final manuscript. EB prepared the final manuscript. EB prepared all table and figures. SH and SO assisted with statistical analysis. All authors reviewed the final manuscript, tables and figures prior to submission. All the authors confirm they have full access to all of data in the study and accept responsibility to submit for publication.

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Figures

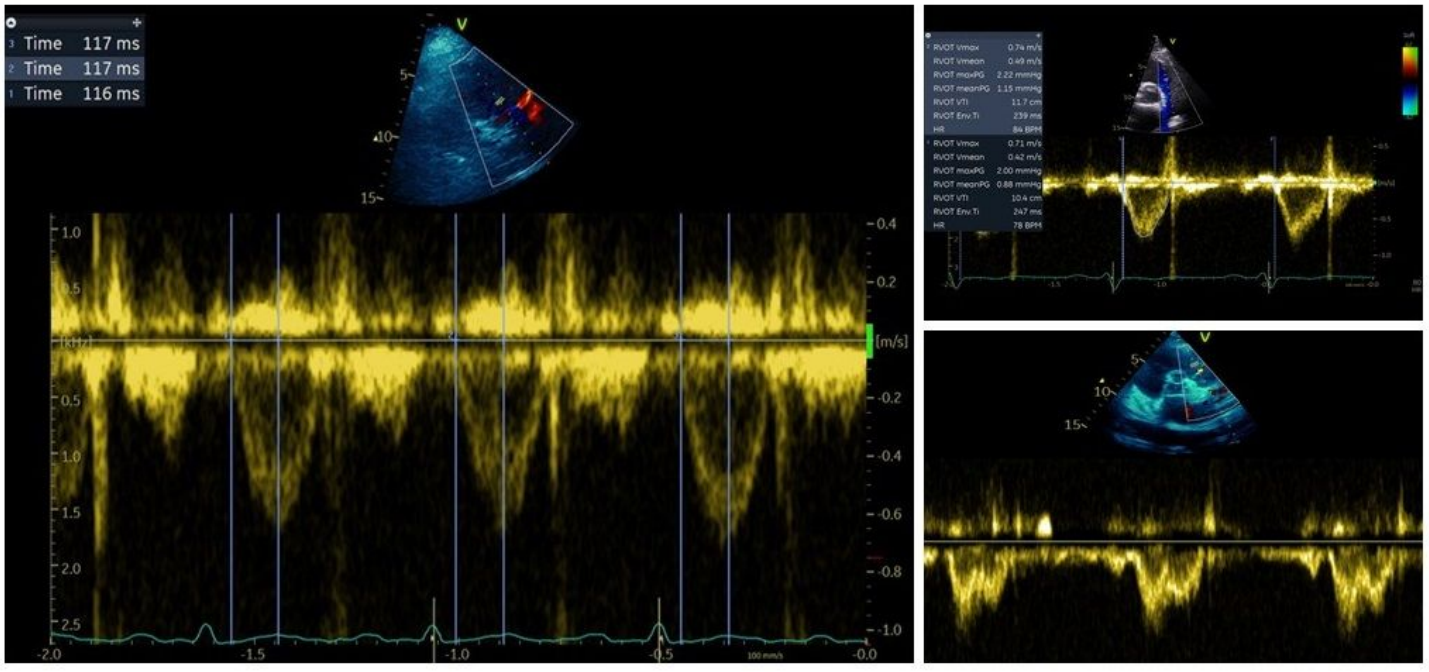

Figure 1

RVOT PWD profile. Left: Measurement of PAAT. Top right: RVOT VTI and ET (RVOT Env Ti). Bottom right: “Notched” waveform showing MSN.

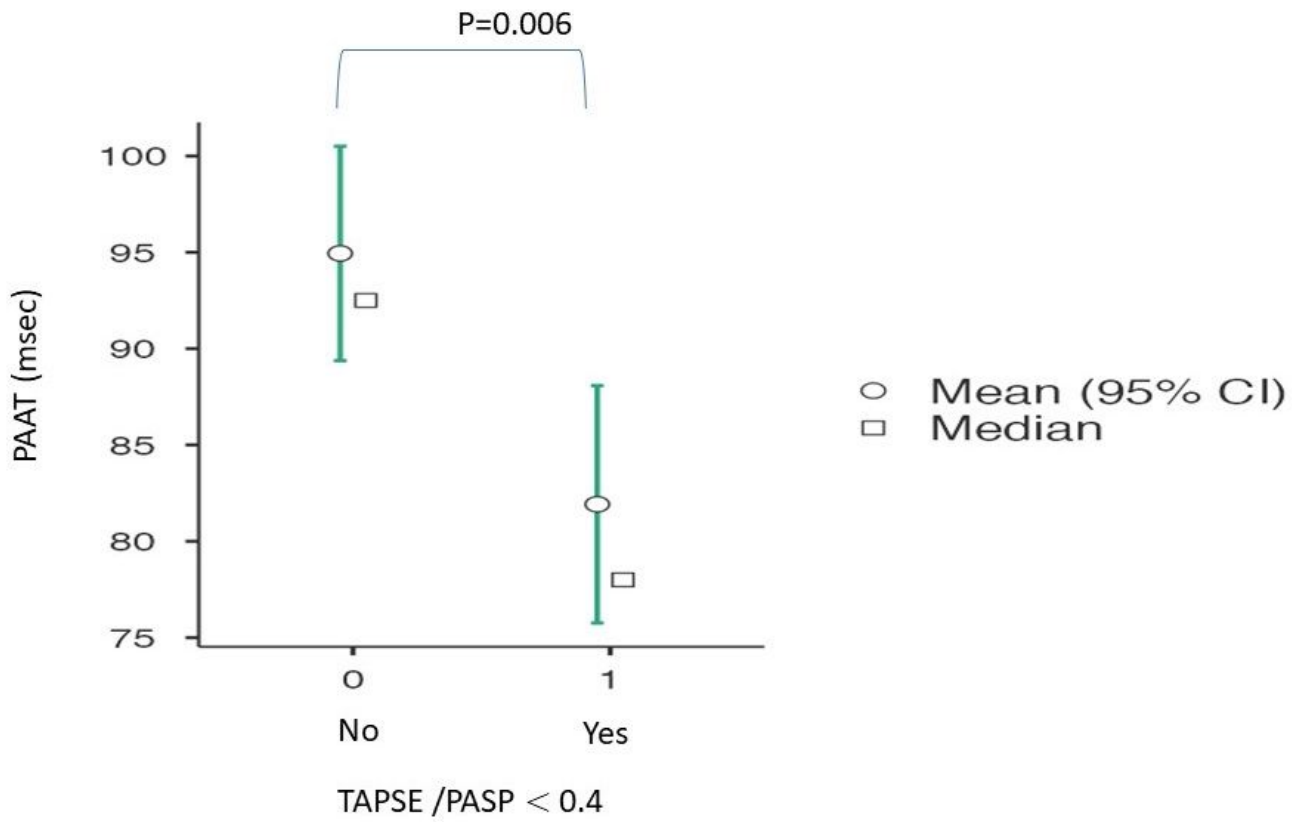

Figure 2

Association of RV-PA uncoupling and PAAT (msec). PAAT is reduced with RV-PA uncoupling (TAPSE/PASP < 0.4); 82±16 v 95±21msec, p=0.006. Mean ± standard deviation and median.

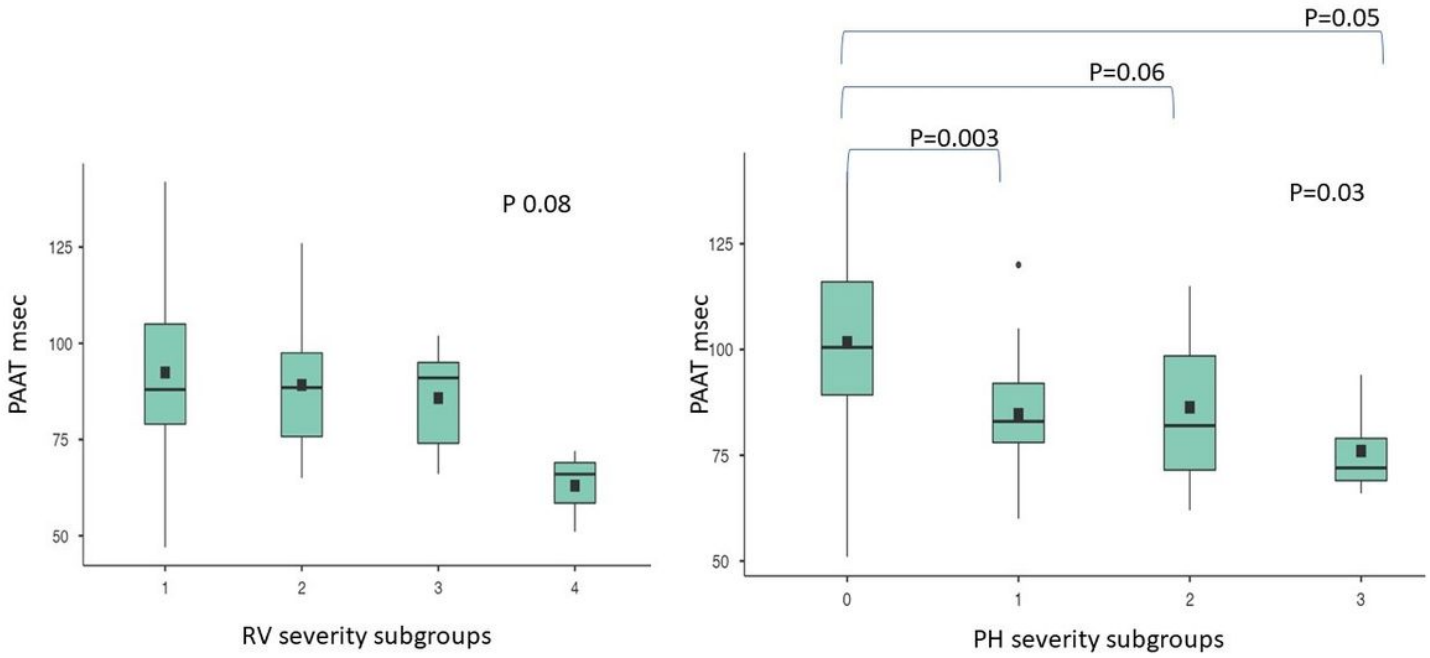

Figure 3

Association of RVD severity by subjective assessment and PAAT (msec). RV function group 1=normal, 2 = mild, 3= moderate, 4= severe. Association of PH severity groups and PAAT (msec), . Error bars ± standard deviation. PH group 0=normal, 1 = mild, 2= moderate, 3= severe

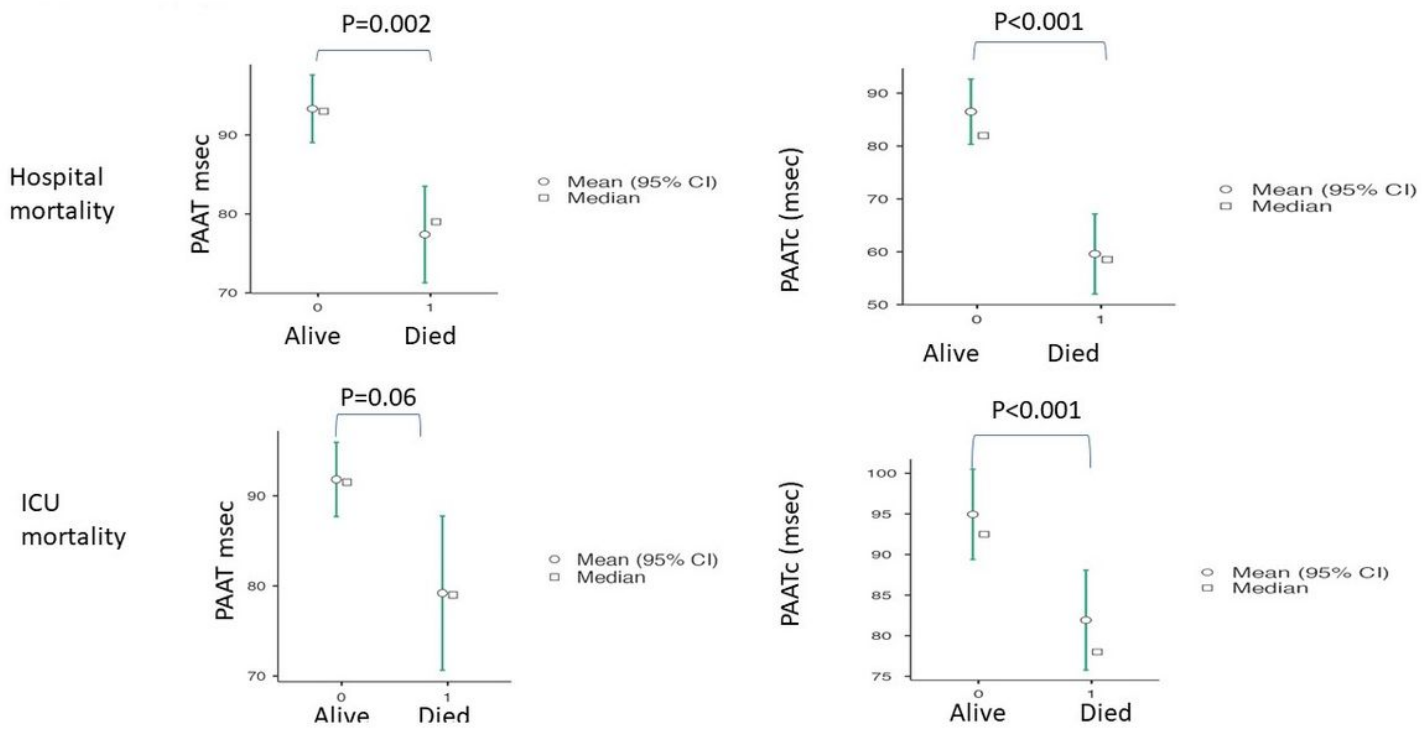

Figure 4

PAAT and PAATc and ICU and hospital mortality. ICU mortality: PAAT(msec) 79±14 v. 92±21, p=0.06. PAATc (msec) 56±16 v. 85 ±29,p<0.001. Hospital mortality: PAAT (msec) 79 ± 14 v. 93±21,p0.002. PAATc(msec) 60±16 v. 87±30, p<0.001.

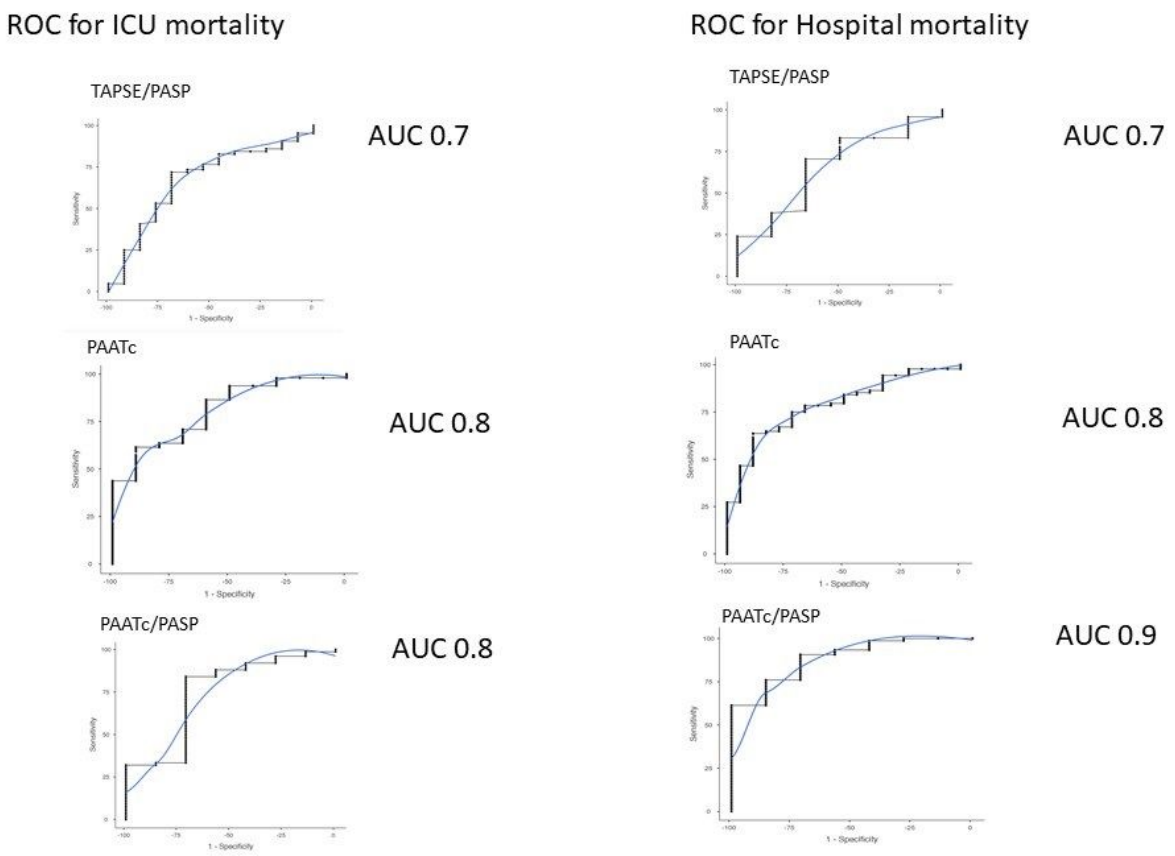

Figure 5

Receiver operating curves for ICU and hospital mortality for TAPSE/PASP, PAATc and PAATc/PASP.

Supplementary Files

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- GraphicalAbstract.jpg