

Pulmonary Artery and Central Venous Pressures as Prognostic Indicators of Post Lung Transplant

Outcome

Kei Togashi

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Miriam Treggiari

Steven Zeliadt

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University of Washington

Abstract

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Kei Togashi

Chair of the supervisory committee:

Miriam Treggiari, MD PhD MPH

Professor, Anesthesiology

Adjunct Professor, Epidemiology

Adjunct Professor, Neurological Surgery

Epidemiology

Background

The relationship between elevated mean pulmonary arterial pressure (mPAP) and central venous pressure (CVP) on poor prognosis in patients undergoing lung transplants has been widely debated.

We hypothesized that not only the isolated values of mPAP and CVP, but also the combination of discordant values in these variables may represent an unfavorable condition in lung transplantation.

Methods

We retrospectively reviewed 80 consecutive patients undergoing lung transplantation between 2008 and 2010. We investigated the relationship between of increased mPAP, CVP, and the discordance of the two variables (discordance group; DG vs. concordance group; CG) on the lowest PO_2/FiO_2 (P/F)

ratio in the first 24 hours after admission to the ICU. We also assessed the impact of these indicators on ventilation time, ICU and hospital length of stay (LOS).

Results

Of the subjects in this study, 70 patients had bilateral lung transplantation, 40 were male, and the mean age was 51.2 (\pm 14.5). All were intubated at ICU admission.

For 1 mmHg increase in mPAP and CVP, the P/F ratio was 5.1 (95% CI 1.06, 9.12) and 8.48 (95% CI 2.89, 14.07) lower respectively. One mmHg increase in mPAP was also associated with hypoxia (defined as P/F ratio < 200), (OR 1.12; 95%CI 1.02-1.23), prolonged mechanical ventilation (MV) (>27hrs) (OR 1.13; 95%CI 1.02-1.25) and ICU LOS (>5 days) (OR1.19; 95% CI 1.06-1.33). One mmHg increase in CVP was also associated with prolonged ICU LOS (OR1.19; 95% CI 1.04-1.37). DG was associated with prolonged ICU LOS compared to CG (OR 6.95; 95% CI 1.37-35.23).

Conclusion

Post-operative mPAP, CVP as well as the interaction of the two have prognostic values in patients undergoing lung transplantation.

Introduction

Since 1963[1], lung transplantation has been used to treat end-stage pulmonary vascular and parenchymal disease. It is estimated that over 32,000 procedures have been performed worldwide[2]. Yet long-term morbidity and mortality still have room for improvement as evidenced by median survival rate of 5.5 years, and unadjusted survival rates of 88% at one year, 64% at 3 years, 53% at 5 years, and 30% at 10 years[2]. Currently, for patients undergoing lung transplantation surgery, primary graft dysfunction (PGD) remains a major cause of morbidity post operatively. PGD increases the risk of bronchiolitis obliterans syndrome, which is known to be the most common cause of long-term morbidity and mortality after lung transplantation [3, 4], resulting in prolonged ventilation time, extended Intensive Care Unit (ICU) and hospital stays, and increased hospitalization costs [2, 5-10]. Currently, PO_2/FiO_2 (P/F) ratio is used as a criteria to diagnose PGD along with chest radiograph assessments [11-14]. Previous studies have assessed the association between elevated mean pulmonary arterial pressure (mPAP) or central venous pressure (CVP) and PGD [15-18]. Based on these results, there has been an effort to develop a guideline for hemodynamic and respiratory management on lung transplant patients aimed towards early detection focused and aggressive treatment of PGD [19].

In previous studies, pre-implantation mPAP was used as a prognostic indicator [15, 16] reflecting the pathology of the diseased lungs, but the prognostic value of mPAP and

CVP representing the newly transplanted lung(s) is incompletely understood.

We hypothesized that not only the isolated values of mPAP and CVP, but also the combined effect of these variables may influence postoperative outcomes for the following reasons: 1) low mPAP in conjunction with high CVP may represent right sided heart failure, whereas high mPAP in conjunction with low CVP may represent persistent pulmonary hypertension after transplantation; 2) high mPAP in conjunction with high CVP may represent hypervolemia and/or excessive vasoconstriction, whereas low mPAP in conjunction with low CVP may represent hypovolemia and/or vasodilation. For post-operative management following lung transplantation, the former physiology is more difficult to treat than the latter. This is because treatment modalities are limited for persistent pulmonary hypertension and right ventricular failure post lung transplantation. For this reason, we hypothesized that discordance in the levels of CVP and mPAP (DG) might be associated with a worse prognosis compared to concordance of the two levels (both levels low or elevated, CG). Therefore, the aim of this study is to evaluate the effect of post transplant mPAP and CVP as well as the joint effect of these variables on post-operative outcome.

Material and Methods

Study design

We conducted a retrospective observational study using clinical data extracted from the University of Washington Medical Center's electronic medical record system. Data was extracted by two different research assistants and later confirmed by the clinician investigator for any missing or inaccurate data.

Study population

A total of 80 consecutive patients who underwent either single-lung or bilateral-lung transplantation procedures between January 2008 and December 2010 were included in the study. All lung transplant candidates met the eligibility criteria for surgery based on guidelines by the international society for heart and lung transplantation (ISHLT) [20].

Surgical technique and operative management

We reviewed medical records to confirm that all bilateral lung transplants were performed through anterior clamshell incision of the chest, and single lung transplant through lateral thoracotomy. Records were reviewed to confirm that all donor lungs were selected according to University of Washington protocol, which included $\text{PaO}_2 \geq 325\text{mmHg}$, normal chest x-ray image, negative history of fungal infection, negative bronchoscopic findings, age ≤ 55 yrs, no smoking history, and time on ventilator ≤ 5 days as its criteria. When one or more of this criteria was not met, donor lung(s) utilization was decided at the clinician's discretion. Donor lungs were preserved in low-potassium, extracellular-type preservation fluids. Cardiopulmonary bypass was used for patients with hypoxia, severe

pulmonary hypertension, patients who did not tolerate one lung ventilation and in cases of hemodynamic instability. Nitric oxide was used in all cases. Inotropes, vasoconstrictors, and fluid administration were initiated to maintain a mean arterial pressure above 60 mmHg, and a cardiac index above 2.0 ml/min/m².

Postoperative management

We confirmed that all patients followed standard postoperative management protocols which included transfer to the ICU for weaning of mechanical ventilation (MV). The protocol for weaning of MV support included stepwise reduction of pressure support and positive end-expiratory pressure of 5 mmHg, and FiO₂ <40%, as tolerated. Immunosuppression drugs were administered as follows: prednisone 1mg/kg PO, cyclosporine 5mg/kg PO preoperatively, methylprednisolone 1-1.5 g and Basiliximab 20mg IV was started intraoperatively, mycophenolate 1g IV q12 hrs and cyclosporine 3-4 mg/hr for a goal blood level of 200-250 ng/ml was started postoperatively, and cyclosporine was transitioned to tacrolimus 0.05mg/kg/day PO as soon as there were signs of return of intestinal function.

Primary endpoint

The primary endpoint was lowest PO₂/FiO₂ ratio in the first 24 hours after admission to the ICU. We dichotomized the data by lowest P/F ratio ≥ 200 or < 200 within 24 hrs after ICU admission. This cutoff value was selected according to previously published studies on

primary graft dysfunction [5, 21].

Secondary endpoints

Secondary endpoints were ventilation time, ICU and hospital length of stay (LOS) or death before discharge from the hospital. More than 24 hours was chosen as the cutoff for prolonged MV. Extended ICU and hospital LOS were defined as more than 5 and 15 days respectively.

Predictors

Hemodynamic variables were extracted from the electronic medical record at the time of ICU admission, and also 24 hours after admission. The predictors included mPAP, CVP and the combination of the two variables at the time of ICU admission. High mPAP was defined as $mPAP \geq 25\text{mmHg}$ according to the definition of pulmonary hypertension from previously published guidelines [22]. High CVP was defined as $CVP \geq 12\text{mmHg}$ according to the recommendation suggested by ISHLT [23]. We also compared these with a receiver operator curve (ROC) analysis to determine the 90% specificity value for mPAP and CVP. ROC was assessed for the relationship between the two predictors (mPAP and CVP) and the lowest P/F ratio in the first 24 hour..

All study procedures were reviewed and approved by the University of Washington's Institutional Review Board.

Statistical Analysis

This is a pilot study to explore the prognostic value of hemodynamic factors for patients undergoing lung transplantation. We examined the univariate association of patient characteristics, surgery type, descriptive indicators of critical care management and surgery (intravenous fluid administration, transfusion products, and chest tube output and use of cardiopulmonary bypass) with our primary endpoint postoperative oxygenation dichotomized as lowest P/F ratio above or below 200 using two-sample Student *t* test for continuous data, with assumption of unequal variance (Satterthwaite's degrees of freedom), and chi-square test for categorical data.

Unadjusted differences in hemodynamic variables at the time of admission were assessed across the primary and secondary endpoint variables using Student *t* test for mPAP and CVP, and the chi-square test for discordance between mPAP and CVP. Linear regression was used to describe the association between mPAP and CVP and postoperative oxygenation.

Multiple logistic regression was used to explore postoperative oxygenation, as well as our other secondary endpoints, adjusting for patient characteristics including age, gender, ASA physical status, surgical type (bilateral/single lung transplant), weight and height as confounding variables. Multiple linear regression was used to assess the association between increases in mPAP or CVP and the outcome variables. For all analyses, a two-sided significance level of .05 was used. All statistical analyses were performed using

STATA version 11.0 (Statacorp; College Station, Texas)

Results

Among the 80 subjects undergoing lung transplant that we identified, 10 had single and 70 had bilateral procedures. The mean mPAP and CVP at admission was 17.9 (\pm 5.9) mmHg and 7.4 (\pm 3.9) mmHg respectively. Overall, we identified 11 discordant pairs with high mPAP suggestive, and low CVP suggestive of persistent pulmonary hypertension or low mPAP and high CVP suggestive of right heart failure.

Table 1 presents the baseline characteristics of participants dichotomized by low postoperative oxygenation (P/F ratio <200), and high postoperative oxygenation (P/F ratio \geq 200) in the first 24 hours after ICU admission.

According to our ROC curves, maximum sensitivity and specificity was detected at cutoff values of 26 mmHg for mPAP and 12 mmHg for CVP. This correlated with the initially set cutoff values for determining discordance of the two variables.

Association between predictors and postoperative oxygenation.

Average mPAP and CVP for the subjects with P/F ratio \geq 200 and P/F ratio <200 were comparable not significantly different (Table 1). In univariate analysis, each 1 mmHg increase in mPAP and CVP at admission was associated with lower postoperative P/F ratio by 5.1 (95% CI 1.06, 9.12) and 8.48 (95% CI 2.89, 14.07) respectively (Figure 1). In multivariate logistic regression, with hypoxia defined as lowest P/F ratio <200 in the first 24

hrs after admission, each 1 mmHg increase in mPAP was associated with 1.12 higher odds of developing hypoxia (OR 1.12; 95%CI 1.02, 1.23), whereas there were no significant association between CVP and hypoxia (OR 1.1; 95%CI 0.98, 1.27). When we compared the DG vs. CG there was a tendency towards higher risk of developing hypoxia in the DG (OR 1.52; 95% CI 0.4, 5.7).

Association between predictors and time on ventilator

The average mPAP and CVP was higher in patients who spent more than 27 hours on MV (19.3 ± 5.8 vs. 16.4 ± 5.5 and 7.7 ± 4.1 vs. 7.0 ± 3.8 respectively). The ratio of DG was also higher in the prolonged MV group (16.7% vs. 10.5) (Table 2). Using multivariate logistic regression, we observed that each 1 mmHg increase in mPAP was associated with increased odds of prolonged MV (>27 hours) (OR 1.13; 95%CI 1.02, 1.25), whereas no association was detected between increase in CVP and prolonged MV (OR 1.05; 95% CI 0.92, 1.2). There was also no association between DG vs. CG and the odds of prolonged ventilation (OR 4.18; 95%CI 0.75, 23.27).

Association with predictors and length of ICU and hospital LOS

The average mPAP and CVP was higher in patients with extended ICU LOS (20.0 ± 5.3 vs. 16.1 ± 5.7 and 8.5 ± 3.6 vs. 6.4 ± 4.1 respectively). The proportion of DG was also higher among patients with extended ICU LOS (24.3% vs. 4.6%). As for hospital LOS, the average mPAP and CVP were both higher in patients with extended length

of stay (18.2 ± 6.0 vs. 17.6 ± 5.7 and 7.8 ± 4.0 vs. 7.0 ± 3.9 respectively). The proportion of DG was also higher in the extended LOS group (20% vs. 7.5%) (Table 2). In multivariate logistic regression, higher levels of mPAP or CVP were associated with extended ICU LOS or death (OR=1.22; $p=0.001$ and OR=1.05; $p=0.007$ respectively) (Table 3). DG also had a higher risk of staying in the ICU longer compared to CG (OR=6.04; $p=0.03$), and there was a trend towards a longer hospital stay in the DG compared to the CG (OR=4.95; $p=0.06$) (Table 3).

Association with predictors and in-hospital mortality

There was no association between mortality and higher levels of mPAP or CVP or between mortality and DG and CG levels.

Discussion

In this study, we observed the association between higher levels of mPAP and hypoxia (P/F ratio <200) (OR=1.12; $p=0.02$), prolonged MV (>27 hours) (OR=1.12; $p=0.02$) as well as extended ICU LOS (> 5 days) (OR=1.22; $p=0.001$). CVP was also associated with extended ICU LOS (OR=1.21; $p=0.007$) as well as hospital LOS (OR=1.15; $p=0.04$). Discordance of the two predictors was also associated with longer ICU stays (OR=6.04; $p=0.03$), with a tendency of extended hospital stays (OR=4.95; $p=0.06$). The multivariate logistic regression results confirming the relationship between mPAP and hypoxia, prolonged MV time as well as extended ICU LOS correlates with previous literatures reporting the association between pulmonary artery pressures and PGD [7, 15, 16, 24] but

differs from what King et al. reported where they did not find any association between postoperative pulmonary artery pressure and reperfusion injury [7].

We also assessed the relationship between the two predictors (mPAP and CVP) and its effect on outcome. Although these variables have been studied individually in the past [15-17, 19, 25], to our knowledge, this is the first study to hypothesize that the discordance of the two variables will have a worse clinical outcome in patients undergoing lung transplantation

In this study we assumed that the mPAP measured after the transplantation will hold an equally prognostic value compared to the preoperative measurement as was the case in previous literatures [15, 16] since it reflects the pulmonary pressure of the newly implanted lung(s). A similar suggestion was made by Sommers et al. [24], though in this study patients all underwent single lung transplantation, and found preoperative pulmonary pressures had no prognostic value. It can be postulated that previous studies linking preoperative pulmonary hypertension to poor clinical outcomes may be due to right ventricular hypertrophy (RVH) which developed through chronically increased pulmonary vascular resistance. With the RVH persisting post operatively, the patients may have generated exceedingly high perfusion pressure, resulting in pulmonary edema after transplantation. For this reason postoperative mPAP measured at the time of ICU admission may serve as a better predictor of clinical outcomes. It is also interesting to note that while higher levels of

mPAP was significantly associated with development of hypoxia, and prolonged MV, increase in CVP was not. This finding differs from previously published results by Pilcher et al. [17] reporting CVP as the prognostic indicator for clinical outcomes following lung transplantation, albeit using different cut off values (the value was 7mmHg in their study). This study eventually resulted in implementation of CVP as an indicator to guide post surgical management developed by Currey et al. [19]. We suggest it may be worthwhile to consider mPAP as an additional indicator.

Contrary to our hypothesis, comparison of DG and CG had no difference in oxygenation measured by P/F ratio nor in MV time. On the other hand, it did have a significant effect on ICU LOS, and a trend towards having a difference in hospital LOS. This may indicate the presence of other factors effecting patient prognosis that is not captured by only measuring P/F ratio.

LIMITATIONS

The presented results are descriptive and hypothesis generating due to the sample size. Future study should be conducted with a larger sample size to determine the generalizability of our findings. As this study is retrospective in nature, the results cannot be interpreted in a cause and effect relationship. For instance, the relationship between increased mPAP and low P/F ratio may have two explanations: 1) non ideal condition of donor lung(s) lead to development of hypoxia, resulting in increased pulmonary vascular

resistance and elevated mPAP; or 2) persistent RVH from long standing pulmonary hypertension led to elevated lung perfusion pressure after lung transplantation, causing pulmonary edema and hypoxia. If suboptimal outcome was for the first reason, treatment should focus on improving donor lung preservation and assessing organ selection criteria. If it was for the second reason, treatment should focus on alleviating right ventricular pressure to avoid excessive perfusion of transplanted lung. Realistically, we can assume poor outcome is a product of a combination of the two. To ascertain which etiology contributes to what degree, further investigation involving a randomized control trial may be warranted.

CONCLUSION

High levels of mPAP and CVP at time of admission, as well as the discordance of these variables at the time of ICU admission had significant association with poor oxygenation, as well as extended ICU and hospital LOS in patients undergoing lung transplantation. Further studies are required to ascertain the etiology behind this observation for use in optimizing clinical management after lung transplantation.

TABLES & FIGURES

Table1: Characteristics of participants by lowest P/F ratio¹

	P/F ratio ≥ 200 (n=50)	P/F ratio <200 (n=30)	p value
Age (years)	52.4 (±14)	49.2 (±15.1)	0.2
Male, n (%)	23 (46%)	17 (56.7%)	0.36
ASA status	3.9 (±0.5)	4.0 (±0.18)	0.68
Height (cm)	168.5 (±10.9)	179.7 (±56.2)	0.91
Weight (kg)	62.9 (±20)	68.2 (±10.3)	0.91
Procedure type			
Single : Bilateral lung transplant	5 : 45	5 : 25	0.38
Crystalloids ¹ (ml)	3053.7 (±2760.5)	3327.8 (±2342.1)	0.67
PRBC ¹ (ml)	1337.7 (±1613.1)	1377.3 (±1792.4)	0.54
FFP ¹ (ml)	130.3 (±420.3)	104.7 (±405.2)	0.4
Plt ¹ (ml)	76.8 (±112.9)	112.4 (±212.4)	0.83
Chest tube output (ml)	1379.1 (±117.3)	1348.4 (±1238.3)	0.46
Use of cardiopulmonary bypass	16 (32%)	16 (53.3%)	0.06
mPAP	16.4 (±5.4)	20.4 (±5.8)	0.99
CVP	6.7(±4.0)	8.6 (±3.6)	0.98
DG (%) /CG (%)	6 (12%)/44(88%)	5(16.7%)/25(83.3%)	0.55

Mean (±SD), ¹ in first 24 hrs after admission to ICU; ASA: American Society of Anesthesiologists; PRBC: Packed Red Blood Cells; FFP: Fresh Frozen Plasma; Plt: Platelet; ICU: Intensive Care Unit

Table 2: Unadjusted comparison of predictors

	Time on ventilator ≤ 27 hrs	Time on ventilator >27 hrs	P values
mPAP	16.4 (±5.5)	19.3 (±5.8)	0.99
CVP	7.0 (±3.8)	7.7 (±4.1)	0.77
DG (%) /CG (%)	4(10.5%)/ 34(89.5%)	7(16.7%)/35(83.3%)	0.43
	ICU LOS ≤ 5 days	ICU LOS > 5 days	
mPAP	16.1 (±5.7)	20.0 (±5.3)	0.99
CVP	6.4 (±4.1)	8.5 (±3.6)	0.99
DG (%) /CG (%)	2 (4.6%)/41(95.4%)	9(24.3%)/28(75.7%)	0.01
	Hospital LOS ≤ 15 days	Hospital LOS > 15 days	
mPAP	17.6(±5.7)	18.2 (±6.0)	0.68

CVP	7.0 (±3.9)	7.8 (±4.0)	0.83
DG (%) /CG (%)	3 (7.5%)/37(92.5%)	8 (20%)/32(80%)	0.11

Mean (±SD), ¹ in first 24 hrs after admission to ICU; ²number (%); mPAP: mean Pulmonary Artery Pressure; CVP: Central Venous Pressure; DG: Discordant Group; CG: Concordant Group

Table 3: Multivariable analysis of risk factors and clinical endpoints

Variable	OR ¹ (95% CI ²)	P value
Association with P/F ratio < 200 in the first 24 hrs		
mPAP	1.12 (1.02, 1.23)	0.02
CVP	1.1 (0.98, 1.27)	0.1
DG vs. CG	1.52 (0.4, 5.7)	0.54
Association with time on ventilator > 24hrs		
mPAP	1.12 (1.01, 1.24)	0.03
CVP	1.08 (0.95, 1.23)	0.25
DG vs. CG	1.39 (0.36, 5.38)	0.64
Association with extended ICU LOS (> 5days) or death		
mPAP	1.22 (1.08, 1.38)	0.001
CVP	1.21(1.06, 1.41)	0.007
DG vs. CG	6.04 (1.16, 31.59)	0.03
Association with extended hospital LOS (> 15days) or death		
mPAP	1.08 (0.98, 1.18)	0.12
CVP	1.15 (1.01, 1.32)	0.04
DG vs. CG	4.95 (0.94, 26.05)	0.06

¹OR: Odds Ratio, Listed OR is risk of clinical endpoints for one mmHg increase mPAP and CVP, as well as DG compared to CG; ²CI: Confidence interval

*Multivariate analyses were adjusted for age, gender, ASA physical status, surgical type (bilateral/single lung transplant), weight and height

**Since the calculated risks are odds ratios and not relative risks, the results should be interpreted as ratio of the probability of each outcome and not as comparison of prevalence.

Figure 1a: Linear correlation of mPAP and lowest P/F ratio in 24 hrs after ICU admission

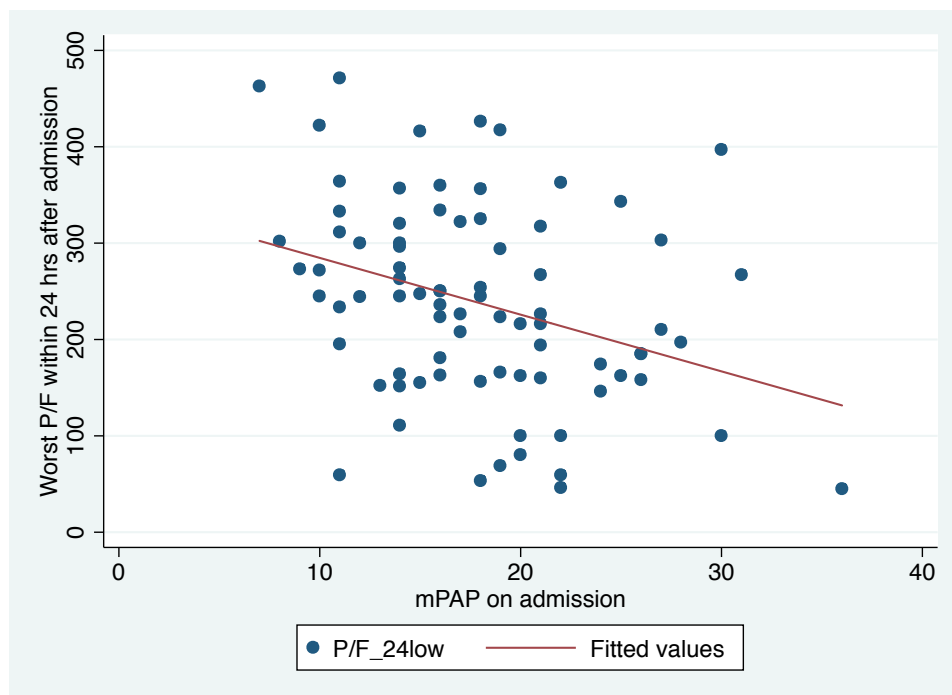
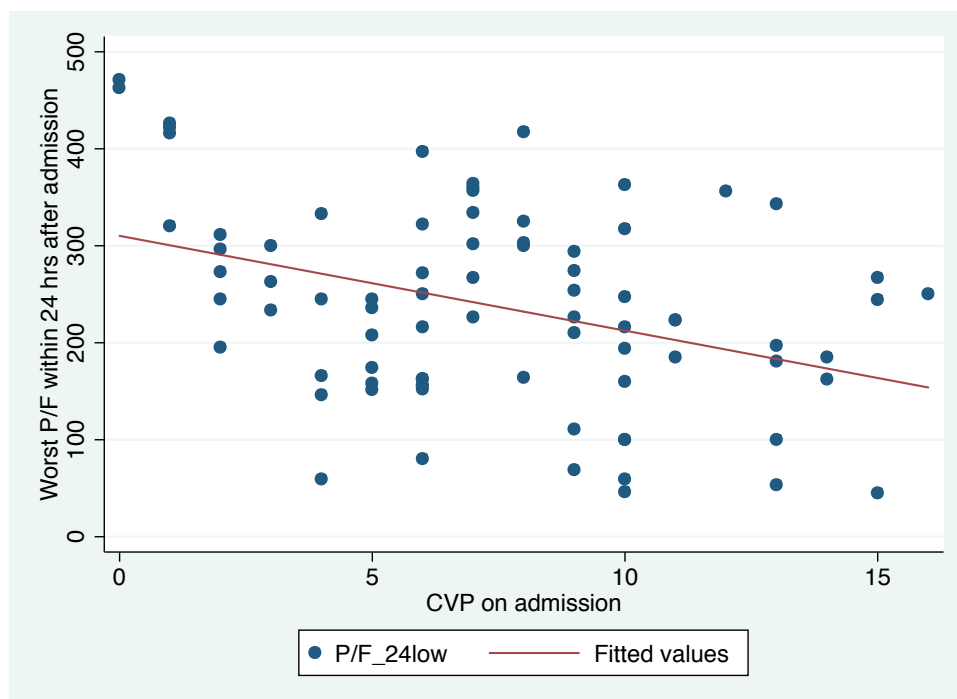


Figure 1b: Linear correlation of CVP and lowest P/F ratio in 24 hrs after ICU admission



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