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# Application of dynamic pulse pressure and vasopressor tools for predicting outcomes in patients with sepsis in intensive care units

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ABSTRACT

*Purpose:* We aimed to determine whether the combination of dynamic pulse pressure and vasopressor (DPV) use is applicable for mortality risk stratification in patients with severe sepsis. We proposed the use of the DPV tool and compared it with traditional sepsis severity indices.
*Materials and methods:* All adult patients who met the sepsis criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) between August 2013 and January 2017 were eligible for the study. Patients who expired within 3 days of admission to the intensive care unit (ICU) were excluded. The primary outcomes were 7-day and 28-day mortality.
*Results:* The study participants included 757 consecutive adult patients. A subpopulation of 155 patients underwent immune profiling assays on days 1, 3, and 7 of ICU admission. The DPV tool had a better performance for predicting 7-day mortality (area under curve, AUC: 0.70), followed by the Sequential Organ Failure Assessment (SOFA) (AUC: 0.64), the plus pulse pressure (AUC: 0.64). For predicting 28-day mortality, the DPV tool was not inferior to the SOFA (AUC: 0.61), DPV tool (AUC: 0.59).
*Conclusions:* The DPV tool can be applied for 7-day and 28-day mortality risk prediction in patients with sepsis.


## 1. Introduction

Sepsis is a syndrome with life-threatening organ dysfunction due to an aberrant or dysregulated host response to infection. Septic shock is a subset of sepsis associated with a greater risk of mortality than that of sepsis alone [1] and patients with septic shock usually require vasopressor treatment to maintain their blood pressure. Sepsis and septic shock remain the dominant causes of death in intensive care units (ICUs), with a wide range of mortality risk depending on the severity of illness and the immune response of patients [2,3]. Despite advances in the management of sepsis, the mortality rate of patients with septic shock continues to be 40–60% [4]. Indices such as the Sequential Organ Failure Assessment (SOFA) score and the quick-SOFA (q-SOFA) score have been proposed for evaluating the severity of sepsis in different settings.

Pulse pressure is defined as the difference between the systolic and diastolic blood pressure. It is derived from the interaction of cardiac ejection and the properties of arterial circulation [5]. A wide pulse pressure range is associated with increased cardiovascular mortality [6] but it has been suggested to be a potential prognostic indicator of decreased mortality among patients with sepsis in a retrospective electronic medical record review [7]. In clinical practice, pulse pressure variation can help predict fluid responsiveness in patients [8,9]. Studies on the relationship of dynamic pulse pressure changes after sepsis treatment are limited.

Our study aimed to determine whether integration of dynamic pulse pressure and vasopressor (DPV) use in scoring represent better measures to predict outcomes in ICU patients with sepsis. We proposed use of the DPV tool and the delta pulse pressure (ΔPP) tool and compared these with traditional sepsis severity indices. Moreover, the subpopulation of patients enrolled for the immune status and cytokine

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study were also analyzed to determine how the host immune response to sepsis plays an important role during progression [10-13].

## 2. Materials and methods

### 2.1. Setting

This study was conducted in 3 medical ICUs (total 34 beds) at the Kaohsiung Chang Gung Memorial Hospital, a 2700-bed tertiary teaching hospital in Southern Taiwan. The hospital is a part of an integrative research program, combining prospective observational and retrospective medical record review, investigation of clinical factors, biomarkers, and patient immune response to predict outcomes of patients with sepsis. Data from this study population were also analyzed for previous aims [14,15]. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Written informed consent was obtained from all patients, or from their surrogates, who prospectively participated in immune profiling and cytokine analysis.

### 2.2. Definitions and study design

All patients who met the sepsis criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [16] between August 2013 and January 2017 were eligible for the study. Patients who expired within 3-days of ICU admission were excluded (Fig. 1). The primary outcomes were 7-day and 28-day mortality.

### 2.3. Data collection

Clinical data retrieved from medical records included age, sex, scoring indices, Charlson comorbidity index, underlying comorbidities, and other clinical factors that were potentially related.

### 2.4. Scoring indices

Systemic inflammatory response syndrome (SIRS) is an inflammatory state that affects the whole body (e.g. body temperature, pulse rate, respiratory rate, white blood count) and can be used for early detection of sepsis [17,18]. The Acute Physiological Assessment and Chronic Health Evaluation II (APACHE II) model has been used since 1985 for classifying illness severity and predicting hospital mortality [19,20].

The q-SOFA score was proposed to identify sepsis and septic shock in patients with suspected infection with 2 of the following 3 criteria: respiratory rate ≥ 22/min, altered mentation, or systolic blood pressure ≤ 100 mmHg [21].

The SOFA score is a means of identifying sepsis among patients who are critically ill with suspected infection. The SOFA score evaluates 6 systems (respiratory, coagulation, liver, cardiovascular (CV), central nervous system [CNS], and renal) [16,22,23].

For the ΔPP Tool, patients were divided into the plus pulse pressure (PP) group (ΔPP [+], value of pulse pressure on day 3 greater than day 1) and the minus pulse pressure (MP) group (ΔPP [−], value of pulse pressure on day 3 less than or equal to day 1).

The DPV tool was used to classify patients into 4 groups: independent on or tapering vasopressor use on day 3 and PP (IVPP); independent on or tapering vasopressor use on day 3 and MP (IVMP); dependent on vasopressor use without tapering dosage on day 3 and PP (DVPP); and dependent on vasopressor use without tapering dosage on day 3 and MP (DVMP).

The immune dysfunction score was constructed by independent predictive factors associated with 28-day mortality in sepsis patients. The score included the segmented neutrophil-to-monocyte ratio (SeMo ratio), plasma granulocyte colony-stimulating factor (G-CSF) level, plasma interleukin (IL)-10 level, and monocyte human leukocyte antigen DR (HLA-DR) expression. [15]

### 2.5. Immune status and cytokine study

Plasma and peripheral blood mononuclear cell preparation, measurements of HLA-DR–related monocyte expression, and cytokine levels have been described in our previous papers [15,24].

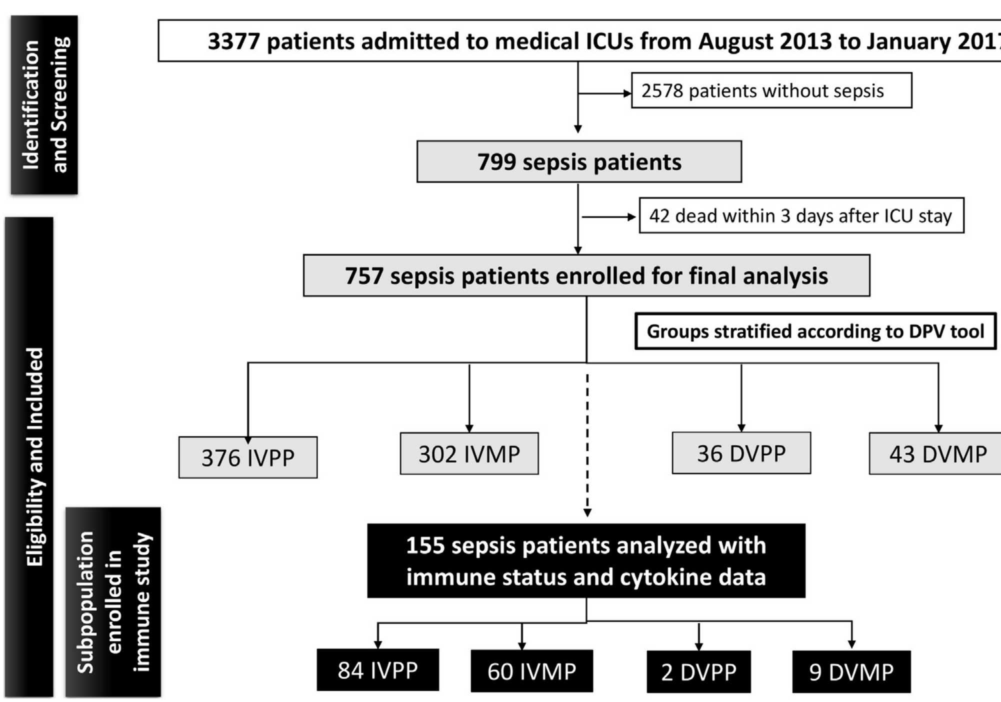


**Fig. 1.** Study flowchart. Abbreviations: DPV tool = Dynamic pulse pressure and vasopressor tool; IV = Independent on or tapering vasopressor use on day 3; DV = dependent on vasopressor use without tapering dosage on day 3; PP = plus delta pulse pressure (value of pulse pressure on day 3 greater than day 1); MP = Minus delta pulse pressure (value of pulse pressure on day 3 less than or equal to day 1).

### 2.6. Statistical analysis

Data analysis was performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA) and statistical significance was set at a two-sided P value < .05. We measured the prognostic accuracy of each severity score using the receiver operating characteristics area under the curve (AUC). AUC comparison was performed using the DeLong method [25] with MedCalc version 18.2.1. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for each score. P values < .05 were considered statistically significant [26]. Patient demographics, clinical characteristics, and outcomes are summarized using frequency and percentage for categorical variables and means with standard deviations as appropriate for continuous variables. Differences between the survivor and non-survivor groups were analyzed using Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables as appropriate. All patient risk factors were analyzed in univariate and multivariate logistic regression for 28-day mortality. Kaplan-Meier analysis was used to determine the effect of the groups on patient survival (7-day, 14-day, ICU, and in-hospital). Comparative analyses among 4 groups (IVPP, IVMP, DVPP, DVMP) were performed using the Pearson chi-square and one-way analysis of variance [27,28].

## 3. Results

### 3.1. Enrolled background

Overall, 3377 patients were admitted to 3 ICUs between August 2013 and January 2017. Exclusion criteria were as follows: (1) patients without a diagnosis of sepsis ($n = 2578$), (2) patients who were < 18 years old, and (3) patients who died within 72 h after admission to the ICU ($n = 42$). Finally, 757 patients with sepsis were enrolled into our study and of these, 155 patients were analyzed for immune profiles (Fig. 1). According to the DPV tool, patients were divided into 4 groups. Patient backgrounds and baseline characteristics of the enrolled patients are provided in Table 1.

### 3.2. Contribution of the DPV tool for prognosis prediction

A multiple logistic regression analysis using a conditional likelihood method was performed to evaluate 6 risk factors (vasopressor requirement on day 1, vasopressor requirement on day 3, APACHE II score, Charlson Comorbidity Index, SOFA score on day 1, and the DPV tool), the cumulative mortality on day 28 for patients in IVPP was the lowest ($P < .001$). In comparison to IVPP, the 28-day mortality risk increased by 27.5% in IVMP, DVPP (HR = 1.878; 95% confidence interval [CI], 0.897–3.944; $P = .096$) and DVMP (HR = 4.660; 95% CI, 2.343–9.269; $P < .001$) (Table 1). The survival curves obtained using Kaplan-Meier analysis stratified patients into 4 groups (28-day survival rate: IVPP, 79.8%; IVMP, 76.2%; DVPP, 61.1%; and DVMP, 39.5%; P < .001) (Fig. 2). Baseline and clinical characteristics for the 757 sepsis patients in the 4 groups determined by the DPV tool are shown in Supplementary Table S1(a) and Supplementary Table S1(b).

### 3.3. Application of the delta pulse pressure

PP group (ΔPP [+]) showed better survival than the MP group (ΔPP [−]) with odds ratio (OR) 1.420 (95%CI: 1.020–1.976) (Table 1). The AUC was 0.544 (95% CI: 0.507–0.580) (Table 2), which was comparable to that when best cut-off value set at 5 mmHg (AUC = 0.561 (0.514–0.607) (Supplementary Fig. S2). Combined with the DPV tool, patients with positive ΔPP had a marginally better outcome (IVPP vs IVMP). Most importantly, in sepsis patients still needing increasing dosage of vasopressor treatment on day 3, the PP group conferred a better survival prediction (DVPP vs DVMP). Patients with increasing dosage of vasopressor use on day 3 (DVPP, DVMP groups) received more fluid

**Table 1**
Baseline characteristics of all patient's risk factors in univariate and multivariate logistic regression in 28-day mortality.

| Baseline characteristics | Non-survival($n = 188$) | Survival ($n = 569$) | Univariate HR (95% CI) | Multivariate HR (95% CI) LR Model |
|---|---|---|---|---|
| Age, years | 66 ± 14.6 | 67 ± 14.9 | | |
| BMI, kg/m$^2$ | 22.6 ± 4.6 | 22.7 ± 5.0 | | |
| Sex, male, n (%) | 114 (60.6) | 332 (58.3) | | |
| APACHE II | 26.0 ± 7.8 | 23.0 ± 8.3 | 1.034 (1.013–1.055)$^a$ | – |
| Charlson comorbidity index | 3.0 ± 2.0 | 2.3 ± 1.9 | 1.179 (1.088–1.278)$^b$ | 1.176 (1.080–1.279)$^b$ |
| Coronary artery disease | 33 (17.6) | 160 (28.1) | | |
| Hypertension | 102 (54.5) | 323 (56.8) | | |
| Liver Cirrhosis | 28 (14.9) | 36 (6.3) | | |
| Diabetes mellitus | 77 (41.0) | 262 (46.0) | | |
| History of stroke | 27 (14.4) | 115 (20.2) | | |
| Chronic kidney disease | 46 (24.5) | 180 (31.6) | | |
| Using vasopressor on day 1 | 60 (31.9) | 140 (24.6) | 1.436 (1.001–2.061)$^a$ | – |
| Using vasopressor on day 3 | 47 (25.0) | 54 (9.5) | 3.179 (2.062–4.902)$^b$ | – |
| $\Delta^{day3\text{-}day1}$ pulse pressure (−) | 98 (52.1) | 247 (43.4) | 1.420 (1.020–1.976)$^a$ | |
| Dependent on vasopressor with increasing dosage on day 3 | 40 (21.3) | 39 (6.9) | 3.673 (2.279–5.919)$^b$ | |
| DPV tool | | | | |
| IVPP | 76 (40.4) | 300 (52.7) | 1$^b$ | 1$^b$ |
| IVMP | 72 (38.3) | 230 (40.4) | 1.236 (0.858–1.780) | 1.275 (0.878–1.852) |
| DVPP | 14 (7.4) | 22 (3.9) | 2.512 (1.228–5.139)$^a$ | 1.878 (0.894–3.944) |
| DVMP | 26 (13.8) | 17 (3.0) | 6.037 (3.117–11.694)$^b$ | 4.660 (2.343–9.269)$^b$ |
| Initial clinical data (day 1) | | | | |
| Systolic pressure, mmHg | 127.1 ± 29.3 | 128.1 ± 29.7 | | |
| Diastolic pressure, mmHg | 71.6 ± 17.6 | 71.5 ± 18.7 | | |
| Pulse pressure, mmHg | 55.5 ± 20.7 | 56.6 ± 22.4 | | |
| MAP, mmHg | 90.1 ± 19.9 | 90.4 ± 20.5 | | |
| SIRS | 2.4 ± 0.9 | 2.2 ± 1.0 | 1.211 (1.028–1.426)$^a$ | – |
| q-SOFA | 1.6 ± 0.6 | 1.5 ± 0.6 | | |
| SOFA scores | 9.9 ± 4.0 | 8.4 ± 3.5 | 1.113 (1.064–1.165)$^b$ | 1.071 (1.018–1.127)$^b$ |

APACHE II score = Acute Physiology and Chronic Health Evaluation score; BMI = body mass index; MAP = mean arterial pressure. Differences between the survivor and non-survivor groups were analyzed using Student's t-test for continuous variables, mean ± (SD) and Chi-square or Fisher's exact test for categorical variables, number (%). $^a$: P value < .05; $^b$: P value < .001.

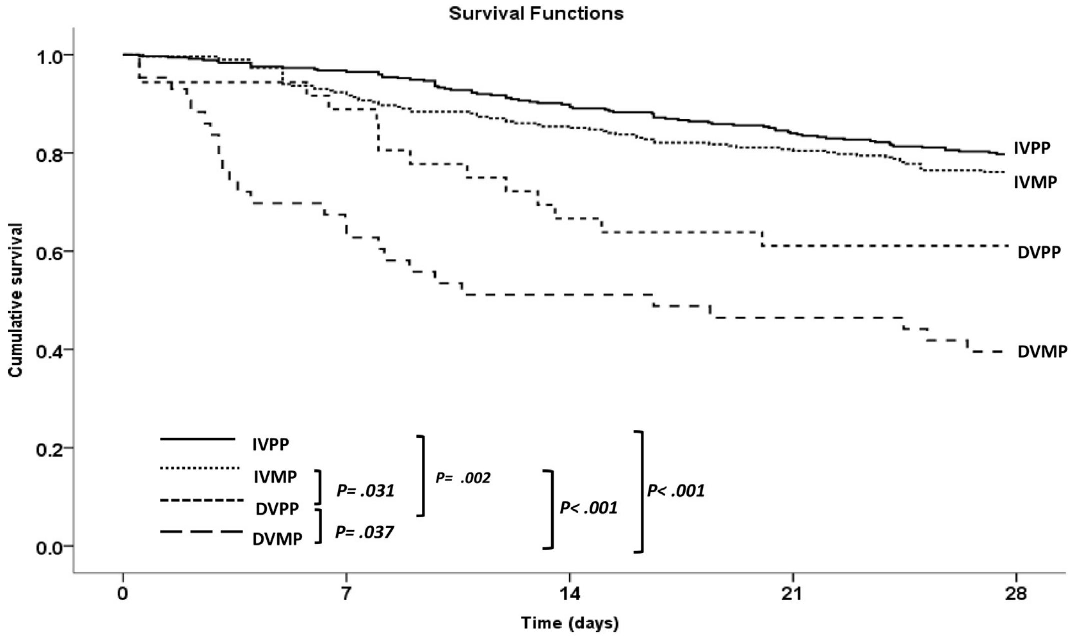


**Fig. 2.** Kaplan-Meier estimates of 28-day survival according to stratification by the DPV tool (n: IVPP = 376, IVMP = 302, DVPP = 36 and DVMP = 43) in 757 sepsis patients. Abbreviations: independent on or tapering vasopressor use on day 3 and PP (IVPP); independent on or tapering vasopressor use on day 3 and MP (IVMP); dependent on vasopressor use without tapering dosage on day 3 and PP (DVPP); and dependent on vasopressor use without tapering dosage on day 3 and MP (DVMP).

resuscitation (Supplementary Table S4). The more positive cumulative fluid balance was associated with a worse outcome.

### 3.4. Comparison of scoring indices

The DPV tool performed well in predicting 7-day and 28-day mortality, as shown in Table 2 and Table 3. The DPV tool (>1) had a better performance for predicting 7-day mortality (AUC: 0.70), followed by SOFA (>11) (AUC: 0.64), ΔPP (>0) (AUC: 0.64), APACHE II (>25) (AUC: 0.62), and q-SOFA (>1) (AUC: 0.57). For predicting 28-day mortality, the DPV tool was not inferior to the SOFA [SOFA >11 (AUC: 0.61), DPV tool >2 (AUC: 0.59), APACHE II >24 (AUC: 0.57), and SIRS >2 (AUC: 0.55)].

### 3.5. Score comparison according to immune profile and dysfunction

Baseline characteristics and clinical laboratory data for 155 sepsis patients with available immune profiles are shown in Supplementary Table S2. The performance of each index and comparisons among indexes for predicting 7-day and 28-day mortality are shown in Supplementary Table S3(a) and Supplementary Table S3(b). Both DPV tool and immune dysfunction score (>1) showed better prediction of 7-day mortality (AUC: 0.74), followed by the ΔPP tool (>0) (AUC: 0.72), and finally, APACHE II (>24) (AUC: 0.64). To predict 28-day mortality, an immune dysfunction score (>1) (AUC: 0.72) had the best performance, followed by the DPV tool (>3) (AUC: 0.63) and SOFA score (>11) (AUC: 0.63).

**Table 2**
7-day and 28-day mortality according to 6 prediction rules in all sepsis patients ($n = 757$).

| Prediction rules ($n = 757$) | Cut-off value | AUC (95% CI) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | NPV (95% CI) | PPV (95% CI) |
|---|---|---|---|---|---|---|
| DPV tool | | | | | | |
| 7-day mortality | >1 | 0.709 (0.675–0.741) [c] | 79.37 (67.3–88.5) | 52.31 (48.5–56.1) | 96.5 (94.5–97.9) | 13.1 (11.5–14.9) |
| 28-day mortality | >2 | 0.593 (0.557–0.628) [c] | 21.28 (15.7–27.8) | 93.15 (90.7–95.1) | 78.2 (76.8–79.5) | 50.6 (40.5–60.7) |
| ΔPP tool | | | | | | |
| 7-day mortality | >0 | 0.641 (0.606–0.675) [c] | 71.43 (58.7–82.1) | 56.77 (53.0–60.5) | 95.6 (93.6–97.0) | 13 (11.2–15.2) |
| 28-day mortality | >0 | 0.544 (0.507–0.580) | 52.13 (44.7–59.5) | 56.59 (52.4–60.7) | 78.2 (75.2–80.9) | 28.4 (25.2–31.9) |
| SIRS | | | | | | |
| 7-day mortality | >1 | 0.554 (0.518–0.590) | 88.89 (78.4–95.4) | 22.62 (19.6–25.9) | 95.7 (91.7–97.9) | 9.4 (8.7–10.3) |
| 28-day mortality | >2 | 0.556 (0.520–0.592) [a] | 55.85 (48.4–63.1) | 57.29 (53.1–61.4) | 79.7 (76.7–82.4) | 30.2 (26.9–33.6) |
| *q*-SOFA | | | | | | |
| 7-day mortality | >1 | 0.576 (0.540–0.611) [a] | 63.49 (50.4–75.3) | 46.97 (43.2–50.8) | 93.4 (91.0–95.2) | 9.8 (8.2–11.7) |
| 28-day mortality | >1 | 0.537 (0.500–0.573) | 57.45 (50.0–64.6) | 47.28 (43.1–51.5) | 77.1 (73.6–80.2) | 26.5(23.7–29.4) |
| APACHE II | | | | | | |
| 7-day mortality | >25 | 0.620 (0.584–0.654) [c] | 61.9 (48.8–73.9) | 58.5 (54.7–62.2) | 94.4 (92.5–95.9) | 11.9 (9.9–14.4) |
| 28-day mortality | >24 | 0.578 (0.542–0.613) [b] | 57.98 (50.6–65.1) | 55.36 (51.2–59.5) | 79.9 (76.8–82.7) | 30 (26.9–33.3) |
| SOFA | | | | | | |
| 7-day mortality | >11 | 0.649 (0.614–0.683) [c] | 49.21 (36.4–62.1) | 77.52 (74.2–80.6) | 94.4 (92.9–95.6) | 16.6 (13.0–20.9) |
| 28-day mortality | >11 | 0.610 (0.574–0.645) [c] | 38.3 (31.3–45.7) | 79.79 (76.3–83.0) | 79.6 (77.6–81.5) | 38.5 (32.9–44.4) |

Data are presented as percentages (95% confidence interval); [a]: *P value* < .05; [b]: *P value* = .001; [c]: *P value* < .001.

**Table 3**
Pairwise comparison of ROC curves (the number represents the *P*-value).

| (*N* = 757) | DPV tool | ΔPP tool | SIRS | *q*-SOFA | APACHE II | SOFA |
|---|---|---|---|---|---|---|
| DPV tool | | *.010*† | *.0003*† | *.002*† | *.061* | *.171* |
| ΔPP tool | .001# | | *.063* | *.179* | *.662* | *.874* |
| SIRS | .241 | .691 | | *.574* | *.178* | *.051* |
| q-SOFA | .064 | .823 | .445 | | *.317* | *.100* |
| APACHE II | .641 | .282 | .500 | .172 | | *.530* |
| SOFA | .575 | .042# | .096 | .014# | .247 | |

*The italics cells represent the *p*-value in pairwise comparison for predicting 7-day mortality; the normal cells represent the *P* value for predicting 28-day mortality.
† Statistically significant difference in predicting 7-day mortality.
# Statistically significant difference in predicting 28-day mortality.

### *3.6. Immune profile patterns stratified by DPV tool*

We divided patients to low and high immune dysfunction groups by immune dysfunction score (Supplementary Fig. S1). Patient distribution and mortality are shown in Fig. 3(a). For the 3 models, ΔPP (−) (compared to ΔPP (+), $P = .056$), DV (compared to IV, $P = .001$), and DVMP (compared to IVMP, IVPP, DVPP, $P < .001$) predicted higher 28-day mortality. In addition to amplifying the stratification power, the immune profile and cytokine study revealed considerable differences among the 4 groups [Fig. 3(b)].

## 4. Discussion

The performance of the DPV tool was better or comparable to more complicated sepsis severity indices. We evaluated consecutive patients with sepsis admitted to the ICU to determine whether a simple and easy DPV tool and ΔPP tool can help predict mortality. We have chosen day-3 cut-off because it is our usual policy of full engagement for a 3-day time frame for most septic patients. The cut-off between early (≤3 days) and late (>3 days) deaths is relevant for refining the prognostic assessment of critically ill patients with septic shock [29]. The DPV tool does not require laboratory workup and can provide valuable outcome prediction.

Infection source control is the cornerstone of treating sepsis. In addition, early treatment with antibiotics and fluids is also important for sepsis management. Survival of patients with sepsis depends on the infection source control, the pattern of organ dysfunction, the underlying comorbidities, and the patient's response to treatment [30]. Our findings are consistent with previous studies demonstrating that respiratory tract infections, particularly pneumonia, are the most common site of infection [31]. The pattern of organ dysfunction can be quantified by the SOFA score and the SOFA sub-score. The DVMP patients had the worst initial SOFA score and SOFA sub-scores, including coagulation and liver and cardiovascular system parameters, and they had the greatest risk for short-term mortality. Using the DPV tool, the 7-, 14-, and 28-day, ICU-, and hospital-survival proportions were significantly different among the 4 groups. The good prediction value may be due to including the patient's response to treatment in the DPV tool (e.g., with comparison of day 3 and day 1 on vasopressor use and pulse pressure). The DPV tool has the advantage of being more convenient than the SOFA score, which needs clinical and laboratory data to calculate.

Early treatment with antibiotic and fluids are the cornerstone of sepsis management [32]. If fluid resuscitation is not adequate, causing insufficient pre-load, systolic pressure will decrease due to decreased cardiac output, resulting in narrow pulse pressure. The condition may worsen due to myocardial function suppression by sepsis. A widened pulse pressure has been suggested as a potential prognostic indicator of decreased mortality in patients with sepsis. However, in the present study, the initial pulse pressure alone cannot discriminate mortality. Patients with increasing dosage of vasopressor use on day 3 (DVPP, DVMP groups) received more fluid resuscitation. Patients with more positive cumulative fluid balance were associated with worse outcome, comparable to the findings of our previous study [33]. Although with a comparable fluid balance and vasopressor use between DVPP and DVMP, survival can be discriminated using the ΔPP tool. Our findings suggest that a positive delta pressure implies better host response to sepsis.

The resolution of inflammation is central to the maintenance of good health and immune homeostasis [34]. Since the progression of cytokines and immune status play an important role in patients with sepsis [35], we delineated the dynamic profile among the 4 groups using the DPV tool. Serum proinflammatory cytokines (G-CSF, IL-6, TNF-α) were highest in the DVMP group on days 1 and 3, suggesting a relationship between hyperinflammation and poor prognosis. On day 3, the concentrations of anti-inflammatory cytokines (IL-1Ra and IL-10) still increased in the DVMP group compared to that on day 1, whereas the levels of those cytokines gradually decreased in both the IVPP and IVMP groups, indicating that the dynamic balance between inflammatory and anti-inflammatory cytokines differed among the 4 patients' groups. No significant difference was observed in terms of HLA-DR level among the 4 groups, but HLA-DR expression percentage was better in the IVPP and IVMP patient groups, which had better survival, suggesting that immune function recovery is important for vasopressor independency and possible survival. The DPV tool appears to facilitate the differentiation of immune profiles. Regarding the relationship between patient stratification by the DPV tool and the immune dysfunction score, there was a potential trend although not statistically significant, which may be due to the small number of patients allocated to the DVPP group.

This study has limitations, including its single-center setting with possible patient-selection bias. However, we provide consistent management, which is important for outcome comparison in patients with sepsis in a very heterogeneous population. Moreover, all consecutive patients with sepsis admitted to designated ICUs were enrolled. The data may not be applied to patients with mild sepsis (not admitted to ICU). We are planning a validation study expanding the sepsis population. The simple measurement of the DPV tool can easily be applied in the hospital ward, although this evaluation was beyond the scope of the study. In addition, we should be aware of the possible prohibitive type 2 error because the percentages of DVPP and DVMP patients were low, especially in subpopulations with immune profiles. To overcome this problem, we are planning to enroll more patients in the validation study. However, the data reflect the reality of clinical practice. DVPP and DVMP patients present more severe sepsis and the ΔPP tool can be helpful. We excluded patients who died within 72 h after admission to the ICU because those patients cannot be classified by DPV tool. However, the patient numbers were relatively small ($n = 42$, including 6 patients with immune data) and their severity scores were very high (mean APACHE II score = 30.9 ± 7.4, SOFA score = 12.4 ± 4.3, immune dysfunction score = 3.3 ± 1.2). The immune dysfunction score can be used on day 1 for prediction, and then the DPV tool can be applied on day 3 for the majority of patients. The strengths of our study include the analysis of subpopulations of patients with a detailed immune profile. In addition, given the relatively large number of consecutive patients

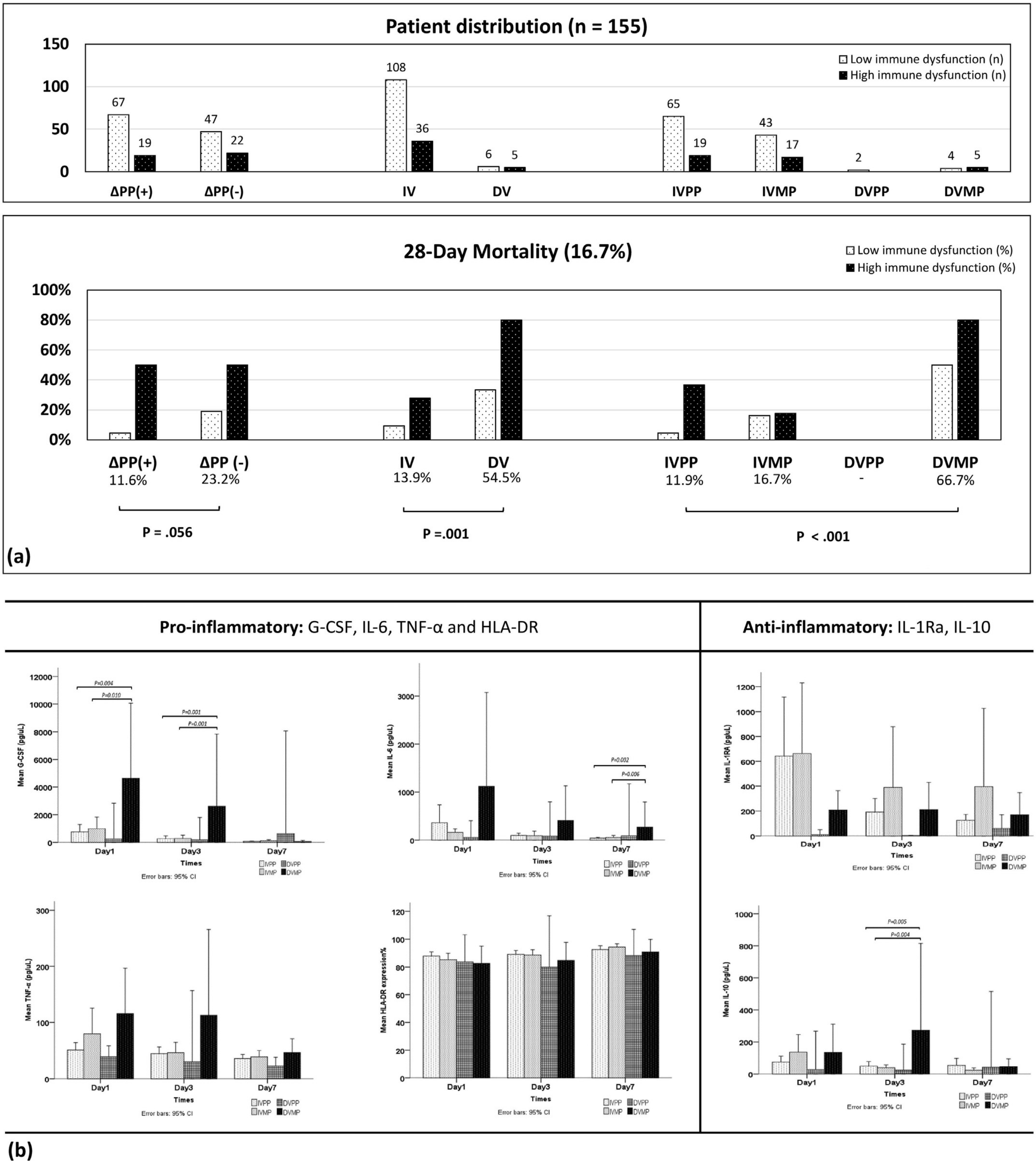


**Fig. 3.** (a). Distribution sepsis patients and 28-day mortality grouped by different models and immune function score. IV = Independent on or tapering vasopressor use on day 3; DV = dependent on vasopressor use without tapering dosage on day 3; ΔPP (+) = Plus delta pulse pressure (value of pulse pressure on day 3 greater than day 1); ΔPP(−) = minus delta pulse pressure (value of pulse pressure on day 3 less than or equal to day 1). (b). Immune status and cytokine expression in subpopulations of patients. G-CSF = granulocyte colony-stimulating factor; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α; IL-10 = interleukin-10; HLA-DR = human leukocyte antigen-antigen D–related expression.

with sepsis enrolled, the characteristics of the patient population were consistent during the entire study period. The comparison of different sepsis scoring indices demonstrated the usefulness of the DPV tool and ΔPP tool. Lastly, our study provides a simple solution for risk stratification in patients with sepsis, associating the immune profile and SOFA.

## 5. Conclusions

The DPV tools can be applied as useful risk assessment tools for patients with sepsis admitted to the ICU.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.003.

## Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. For the patients who prospectively participated in immune profiling and cytokine analysis, written informed consent was obtained from all the patients or their surrogates.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

*Conception or design of the work*

WFF, CCW, MCL.

*Acquisition, analysis, or interpretation of data for the work*

WFF, CHH, YMC, KYH, YCC, CYL, YTF, YTC, HCC, KTH, HCC, YCC.

*Drafting the work and revising it critically for important intellectual content*

WFF, CHH, YHW.

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