

# Plasma vanin-1 as a novel biomarker of sepsis for trauma patients: a prospective multicenter cohort study

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## Research

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# Abstract

## Background

Vanin-1 plays a pivotal role in oxidative stress and the inflammatory response. However, its relationship with traumatic sepsis remains unknown. The aim of our study was to evaluate whether plasma vanin-1 expression can be used to predict traumatic sepsis in an early time.

## Methods

In this three-stage prospective cohort study, severe trauma patients admitted to two hospitals from January 2015 to October 2018 were enrolled. Clinical data during hospitalization and APACHE II score were collected. Plasma vanin-1 levels were measured by enzyme linked immunosorbent assay. The associations among variables and traumatic sepsis were identified by logistic regression model. The receiver-operating characteristic curve was analyzed to evaluate the diagnostic efficiency of the selected factors.

## Results

A total of 426 trauma patients (22 patients in the discovery cohort, 283 patients in the internal test cohort, and 121 patients in the external validation cohort) and 16 healthy volunteers were enrolled. The plasma vanin-1 level of trauma patients was significantly higher than that of healthy volunteers ( $P < 0.05$ ), and sepsis patients had higher plasma vanin-1 than non-sepsis patients in the discovery trauma cohort ( $P < 0.05$ ). In the internal test cohort, plasma vanin-1 levels at day 1 after trauma were significantly associated with the incidence of sepsis (OR = 3.92, 95% CI = 2.68–5.72,  $P = 1.62 \times 10^{-12}$ ). As a predictive biomarker, vanin-1 obtained a better area under the curve (AUC) (0.82, 95% CI = 0.77–0.87) than C-reactive protein (CRP) (0.62, 95% CI = 0.56–0.68,  $P < 0.0001$ ), procalcitonin (PCT) (0.66, 95% CI = 0.60–0.71,  $P < 0.0001$ ), and Acute Physiology and Chronic Health Evaluation II (APACHE II) (0.71, 95% CI = 0.65–0.76,  $P = 6.70 \times 10^{-3}$ ). In addition, the clinical relevance between plasma vanin-1 and traumatic sepsis was validated in the external validation cohort (OR = 4.26, 95% CI = 2.22–8.17,  $P = 1.28 \times 10^{-5}$ ). The AUC of vanin-1 was 0.83 (95% CI = 0.75–0.89), which was better than that of CRP, PCT, and APACHE II.

## Conclusions

Our study demonstrated that plasma vanin-1 increased among trauma patients and was independently associated with the risk of sepsis. Vanin-1 might be a potential biomarker for the early prediction of traumatic sepsis.

## Trial registration

Clinicaltrials.gov Identifier NCT01713205. Registered 24 October 2012.

## Background

Sepsis is one of the most common complications and the leading cause of in-hospital death for severe trauma patients (1, 2). Sepsis results in a longer length of hospital stay and higher health care costs, which greatly increases the burden on society (3, 4). However, the diagnosis of post-traumatic sepsis is notoriously difficult in the sense that trauma patients are in a state of “sterile inflammation” (5). The strong oxidative stress induced by severe injury may produce a genomic storm with an alteration of up to 80% of the leukocyte transcriptome which largely affecting the parameters used to diagnose sepsis (6). Considering the consequences of sepsis after trauma, early recognition and individualized therapy of those patients at high risk of sepsis are essential prerequisites to reduce the morbidity of trauma patients (7, 8). Therefore, finding an ideal biomarker facilitating the early prediction of post-injury sepsis is highly warranted.

Vanin-1 (Vascular non-inflammatory molecule 1, *VNN1*) is a pantetheinase that hydrolyzes pantetheine to pantothenic acid (vitamin B5) and cysteamine. Beyond its function in coenzyme A (CoA) metabolism, *VNN1* has been found to participate in both oxidative stress and the inflammatory response (9, 10). *VNN1*<sup>-/-</sup> mice showed increased tolerance to oxidative stress caused by  $\gamma$ -irradiation or paraquat in toxication (11). In addition, they showed an attenuated inflammatory reaction after infection by schistosomiasis (12) or rickettsiosis (13). In patients with multiple injuries, physical damage is the initiating factor in the production of oxygen free radicals and inflammatory reactions, and numerous studies have demonstrated associations between injury and elevated oxidative stress and inflammation (14). Therefore, we hypothesized that vanin-1 might increase in response to physiological stress in trauma patients and might act as a potential predictive biomarker of traumatic sepsis.

In this multicenter study, we detected the change of plasmavanin-1 levels in trauma patients. Then, we investigated the relationship between vanin-1 expression and incidence of sepsis. In addition, a prospective cohort study was conducted to evaluate the predictive power of plasma vanin-1 for traumatic sepsis. Finally, an independent cohort was conducted to validate these findings. Our aim is to determine whether plasma vanin-1 could act as a potential biomarker for the early diagnosis of sepsis in trauma patients.

# Methods

## Study design and setting

The present study was a two-center, prospective cohort investigation. Severe trauma patients with an Injury Severity Score (ISS) greater than 16 points, admitted to the hospital within 24 hours after injury were enrolled from the ICU at the Department of Trauma Surgery from Daping Hospital and the Centre Hospital of Chongqing University during January 2015 to October 2018. Patients who met one of the following criteria were excluded: 1) age < 15 years old or > 65 years old; 2) pregnancy; 3) malignant tumor; 4) serious chronic history of cardiovascular, respiratory, renal, hepatic, hematologic, or immunological diseases. Sixteen healthy volunteers were asymptomatic nonsmokers under 65 years of age, who had no known chronic medical conditions.

This study includes a discovery cohort and two test cohorts. Patients were followed up during the hospital stay and divided into sepsis and non-sepsis group during data analysis according to the occurrence of sepsis, which was defined as a suspected infection with an acute change in SOFA scores  $\geq 2$  (Sepsis-3) (15). The definition of infection was a clinically obvious source or positive bacterial culture.

The research was approved by the Institutional Ethics Review Board of the Army Medical University. Informed consent of all patients was obtained from the patients or their relatives. The National Clinical Trial number is NCT01713205. Registered 24 October 2012.

## Data Collection

Demographic characteristics and clinical data, including general condition, vital signs and consciousness state were retrieved from the electronic medical records. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Sequential Organ Failure Assessment (SOFA) scores were calculated to evaluate the disease severity and organ failures.

## Detection of Vanin-1 in Plasma

Blood specimens were collected and processed as previously reported (2). Briefly, whole blood was collected using an EDTA-coated tube immediately after admission and kept at 4°C. Sample was centrifuged within 1 hour at 3000 rpm for 5 minutes at 4°C. The plasma was separated and stored at -80°C for further analyses. To test the dynamic change in plasma vanin-1, blood samples at days 1, 3, 5, 7, and 14 after injury were collected in the discovery cohort. The basic levels of plasma vanin-1 were measured among 16 healthy volunteers. A commercially available enzyme-linked immunosorbent assay (ELISA) (Cloud-Clone Corp, USA) was conducted to detect vanin-1 in plasma. Vanin-1 levels were determined in duplicate following the manufacturer's instructions.

## Statistical analysis

Categorical variables were summarized as number and proportion, and the differences were compared with the  $\chi^2$  test. Continuous variables were expressed as the median and inter quartile ranges (IQRs, 25–75th percentiles), and comparisons were performed using Mann-Whitney U test. The associations among variables and traumatic sepsis were identified by logistic regression model. Additionally, we made adjustment with age, sex and ISS to correct the associations. The evaluation of the predictive accuracy was performed using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The correlations between vanin-1 and other variables were assessed using Spearman rank correlation coefficient. The statistically significant differences were  $P < 0.05$ . All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, USA) and MedCalc version 13 (MedCalc Software, Ostend, Belgium).

# Results

## The Clinical data and General Information

In total, 426 patients suffering from severe injury were enrolled in our study, including 305 patients (11 sepsis patients and 11 non-sepsis patients were randomly selected as the discovery cohort, and the remaining 283 patients as the internal test cohort), and 121 patients from Chongqing Emergency Medical Center as the external validation cohort. The age, gender, injuries and infections among three groups were comparable (Table 1). Most patients developed sepsis 3-5 days after injury. Gram-negative bacteria were the main pathogenic microorganisms, while pneumonia and primary bloodstream infections were the major infection sites.

### Table 1. Clinical characteristics of trauma patients

Variables	Discovery cohort (n=22)	Internal test cohort (n = 283)	External validation cohort (n = 121)	P value*
Gender♀Female/Male♂	4/18	59/224	28/93	0.90
Age (years)	44.75±15.02	43.39±12.01	44.48±12.65	0.68
ISS	26.85±9.19	24.45 ± 8.44	22.97±8.56	0.10
AIS <sub>Head/neck</sub>	2.55± 1.76	1.80 ± 1.67	1.80±1.65	0.10
AIS <sub>Face</sub>	0.40± 0.60	0.43 ± 0.79	0.28±0.59	0.12
AIS <sub>Thorax</sub>	3.05± 1.23	2.71 ± 1.26	3.01±1.06	0.43
AIS <sub>Abdomen</sub>	1.65± 1.66	1.26 ± 1.52	1.30±1.32	0.47
AIS <sub>Upper/lower extremity</sub>	1.70± 1.13	2.17 ± 1.49	1.95±1.63	0.07
GCS initial	13.85± 6.16	14.00± 3.00	13.78 ±2.68	0.32
APACHE II scores initial	7.85 ±3.76	7.67 ± 6.31	7.40±4.57	0.92
SOFA scores initial	1.85 ± 1.18	2.95 ± 2.22	2.28±1.41	0.10
Sepsis, n (%)	-	91 (32.16%)	41(33.88%)	0.73
Pathogens, n (%)				0.46
Gram-negative	-	62(68.13%)	21(51.22%)	
Gram-positive	-	11 (12.09%)	8(19.51%)	
Mixed gram-negative and -positive	-	7 (7.69%)	5(12.20%)	
Others	-	4 (4.40%)	2(4.87%)	
Negative blood cultures	-	7(7.69%)	<b>5(12.20%)</b>	
Source of infection, n (%)				0.41
Blood	-	25(27.47%)	10(24.39%)	
Sputum	-	27(29.68%)	13(31.71%)	
Urine	-	15(16.48%)	8(19.51%)	
Secretions	-	18(19.78%)	4(9.76%)	
Others	-	6 (6.59%)	6(14.63%)	
Time trauma-sepsis onset, days	5.85± 2.91	5.76± 4.82	5.03±2.52	0.72
ICU days	6.16±9.22	4.47± 7.92	5.76±13.01	0.99
Deaths	0(0.00%)	9(3.18%)	3(2.48%)	0.66

ISS, injury severity score; AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment.

\*Categorical variables were compared using the  $\chi^2$  test and continuous variables were compared using ANOVA test.

### The dynamic change of plasma vanin-1 after injury

The median plasma vanin-1 levels were 0.63 ng/mL (IQR, 0.52–0.66 ng/mL) for healthy population. Trauma patients had the highest plasma vanin-1 on the first day of admission ( $1.73 \pm 1.07$  ng/ml,  $P=1.21 \times 10^{-4}$ , discovery cohort) (Figure 1A). Then, the level of vanin-1 gradually declined from day 3 to day 14 after injury but was still significantly higher than that of healthy controls ( $P<0.01$  for all days). We further compared plasma levels of vanin-1 between the sepsis and the non-sepsis group. Significantly elevated plasma levels of vanin-1 were found in sepsis patients, especially on early days after admission ( $P=0.03$  for day 1 and  $P=0.04$  for day 3), indicated the potential predictive value of vanin-1 levels for sepsis in trauma patients (Figure 1B). No significant difference was demonstrated between two groups at day 5, 7, and 14.

## Predictive Value of the Plasma Vanin-1 in Trauma Patients

To investigate whether plasma vanin-1 could be used as a predictive biomarker of traumatic sepsis, we evaluated the predictive power of plasma vanin-1 at day 1 in 283 trauma patients (Internal test cohort). Our results showed a strong association between higher plasma vanin-1 levels taken 24 hours post injury and the incidence of secondary sepsis within the subsequent 14 days ( $P=6.02 \times 10^{-13}$ ) (Figure 2A). No significant correlation between ISS and plasma vanin-1 was observed ( $r^2=0.01$ ,  $P=0.06$ ). In addition, our results demonstrated that the level of plasma vanin-1 at day 1 was significantly associated with the incidence of sepsis patients after trauma (OR=3.89, 95% CI=2.68-5.63,  $P=6.99 \times 10^{-13}$ ) (Table S1). Logistical regression analyses also demonstrated that plasma vanin-1 was significantly related to a higher occurrence of sepsis adjusted by age, sex, smoking, drinking, and ISS (OR=3.92, 95% CI=2.68-5.72,  $P=1.67 \times 10^{-12}$ , Table 2). Based on the ROC analysis of plasma vanin-1 at day 1, an AUC of 0.82 (95% CI=0.77-0.87) was obtained for the morbidity of sepsis after trauma (Figure 3A). The optimal cut-off value was 1.41 ng/ml in the internal test cohort with the sensitivity and specificity of 70.00% and 84.90%, respectively (Table S2). Although CRP, PCT, and APACHE II at day 1 after trauma were also associated with the risk of traumatic sepsis in our internal test cohort (Table S1, S2 and Table 2), our results revealed that vanin-1 had a better AUC than other biomarkers (CRP,  $P<0.0001$ ; PCT,  $P<0.0001$ ; APACHE II,  $P=6.70 \times 10^{-3}$ ) (Figure 3A).

**Table 2. Associations between each biomarker and traumatic sepsis in adjusted logistic regression models**

Variables	Internal test cohort		External validation cohort	
	OR (95% CI)	<i>P</i> *	OR (95% CI)	<i>P</i> *
APACHE II	1.17(1.10-1.23)	$5.35 \times 10^{-8}$	1.21(1.08-1.37)	$1.00 \times 10^{-3}$
PCT	1.06(1.02-1.10)	$2.00 \times 10^{-3}$	0.99(0.90-1.08)	0.86
CRP	1.01(1.00-1.01)	$3.00 \times 10^{-3}$	1.01(1.00-1.02)	0.05
Vanin-1	3.92(2.68-5.72)	$1.62 \times 10^{-12}$	4.26(2.22-8.17)	$1.28 \times 10^{-5}$

APACHE II, Acute Physiology and Chronic Health Evaluation II; PCT, procalcitonin; CRP, C-reactive protein.

\*Adjusted by age, sex, smoking, drinking, and ISS.

## The Validation of Vanin-1 for Predicted Sepsis in Trauma Patients

We further validate the predictive ability of plasma vanin-1 at day 1 after injury in the external validation cohort. In this cohort, plasma vanin-1 was also not associated with ISS ( $r^2=0.03$ ,  $P=0.07$ ). Sepsis patients had significant higher plasma vanin-1 than non-sepsis patients at day 1 after injury ( $P=8.39 \times 10^{-6}$ ) (Figure 2B). Plasma vanin-1 at day 1 after injury was also associated with the risk of sepsis, adjusted by age, sex, smoking, drinking, and ISS (OR=4.26, 95% CI=2.22-8.17,  $P=1.28 \times 10^{-5}$ , Table 2). Plasma vanin-1 obtained an AUC of 0.83 (95% CI=0.75-0.89) for the incidence of sepsis after trauma (Figure 3B). The optimal cut-off value was 1.35 ng/ml in the external validation cohort, with a sensitivity and specificity of 70.73% and 90.00%, respectively (Additional file 1: Table S2). We also analyzed the associations between CRP, PCT, APACHE II and traumatic sepsis. Except for the PCT, the remaining CRP and APACHE II were related to the risk of sepsis after trauma (Table 2 and Additional file 1: Table S1). When compared with CRP (AUC=0.59, 95% CI=0.500-0.68,  $P=1.20 \times 10^{-3}$ ), PCT (AUC=0.63, 95% CI=0.54-0.71,  $P=1.30 \times 10^{-3}$ ), and APACHE II (AUC=0.72, 95% CI=0.63-0.80,  $P=0.09$ ), vanin-1 also obtained a better predictive ability (Figure 3B and Table 3). Furthermore, combining plasma vanin-1 with APACHE II increased the diagnostic efficiency (AUC = 0.85, Table 3).

**Table 3. Predictive probability of single predictor in trauma cohort**

Variables	Internal test cohort						External validation cohort					
	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (%)
CRP	0.62(0.56-0.68)	37.36	84.37	53.1	74.0	79.8	0.59(0.50-0.68)	78.05	43.75%	41.6	79.5	3
PCT	0.66(0.60-0.71)	67.03	59.90	44.2	79.3	0.67	0.63(0.54-0.71)	80.49	40.00%	40.7	80.0	0.219
APACHEII	0.71(0.65-0.76)	62.64	69.29	49.1	79.6	6	0.72(0.63-0.80)	78.05	56.25%	47.8	83.3	6
Vanin-1	0.82(0.77-0.87)	70.33	84.90	68.8	85.8	1.41	0.83(0.75-0.89)	70.73	90.00%	78.4	85.7	1.35
APACHE II + Vanin-1	0.85(0.80-0.89)	70.45	86.98	-	-	-	0.87(0.80-0.93)	80.49	87.50%	-	-	-

CRP, C-reactive protein; PCT, procalcitonin; APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value.

## Discussion

Increasing evidence has highlighted the importance of vanin-1 in various cancer and inflammatory disorders, including septic shock (17). However, whether vanin-1 could be used as a biomarker for early warning of traumatic sepsis is still unknown. In this study, elevated admission plasma vanin-1 levels were observed in severe trauma patients. We have demonstrated that increased admission vanin-1 was significantly associated with the incidence of sepsis in severe trauma patients. Furthermore, after adjusted with age, sex, smoking, drinking, and ISS, vanin-1 was strongly associated with sepsis. When plasma vanin-1 was used as a biomarker for the early prediction of traumatic sepsis, better predictive abilities were obtained than PCT, CRP and APACHE II in both of our validate cohorts.

In previous studies, *VNN1* mRNA had been used to predict the risk or prognosis of colorectal cancer (18, 19) and acute myeloid leukemia patients (20). Elevated circulation or urinary vanin-1 has been reported in acute/chronic kidney injury(21, 22), drug-induced renal injury (23) and asthma patients (24). We demonstrated in the current study that plasma vanin-1 increased rapidly after injury. Specially, patients who developed sepsis later have higher plasma vanin-1 on admission. It is consistent with the findings from our group through reanalyzing genome-wide expression of leukocytes from trauma patients in the public traumatic website (The Human Genomic Response to Severe Traumatic Injury, <http://web.mgh.harvard.edu/TRT/>). In this public database, *VNN1* mRNA was upregulated and differentially expressed between the complicated recovery group and the uncomplicated recovery group within 12 hours and at 1, 4, 7, 14, 21, and 28 days after injury. We further analyzed the public transcriptome data of sepsis patients from the GEO dataset (<https://www.ncbi.nlm.nih.gov/gds/>). Upregulation of *VNN1* mRNA in sepsis patients was obviously detected in the GSE28750 (25), GSE64457 (26), and GSE46995 (27).

It has been controversial that whether PCT and CRP can be used to predict the incidence of sepsis in trauma patients (28). In this study, we showed that both PCT and CRP were not suitable for diagnosing sepsis in severe trauma patients, with low sensitivity or specificity. In our two larger trauma cohorts, plasma vanin-1 at day 1 after trauma was independently associated with the incidence of traumatic sepsis even adjusted by age, sex, smoking, drinking, and ISS in the multiple logistic regression analysis. It could predict the risk of sepsis after trauma with an AUC over 0.80. Compared with CRP, PCT, and APACHE II, plasma vanin-1 outperformed the predicted ability in our study cohorts. When vanin-1 was combined with the APACHE II score, the AUC could be increased to 0.85. All of these findings supported vanin-1 increases in trauma patients, and plasma vanin-1 might be used as a potential biomarker of post-injury sepsis at the early stage. The potential relevance of plasma vanin-1 would help clinicians categorize high-risk sepsis patients at the early stage of trauma and enable rapid treatment, improve outcomes, and reduce unnecessary antibiotic therapy.

To our knowledge, little has been known about the mechanisms of how vanin-1 influences the process of sepsis. *VNN1* might play a protective role against oxidative stress and the inflammatory response caused by infection (29, 30). Yamashita *et al.* reported vanin-1 elevation in patients with influenza A (H1N1) pneumonia (31). Furthermore, *VNN1* mRNA increased significantly in the human alveolar epithelial carcinoma cell line A549 in response to TNF- $\alpha$ , IL-6, IL-1 $\beta$ , lipopolysaccharides (LPS) and H<sub>2</sub>O<sub>2</sub>. These studies indicated that the strong oxidative stress caused by injury also induced the upregulation of *VNN1* mRNA. In addition, injury and subsequent pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , might upregulate *VNN1* mRNA levels (31, 32). Additionally, previous studies demonstrated that glutathione, the most potent cellular antioxidant, was elevated in *VNN1*<sup>-/-</sup> mice, resulting in a lack of cysteamine in tissues. Therefore, *VNN1*<sup>-/-</sup> mice exhibited resistance to oxidative damage

and reduced inflammatory responses (11). Moreover, there was a negative correlation between the expression levels of *VNN1* and peroxisome proliferator-activated receptor- $\gamma$  (*PPAR* $\gamma$ ) (33). *PPAR* $\gamma$  in monocytes plays an anti-inflammatory role by inhibiting other transcription factors, such as nuclear factor- $\kappa$ B and activator protein 1 (34, 35). *VNN1* promotes inflammation partly by inhibiting both *PPAR* $\gamma$  expression and signal transduction (32, 33). Lan Ling et al. suggested that *VNN1* was negatively regulated by miR-203 and affected sepsis through AKT signaling pathway. Therefore, we speculated that *VNN1* played an important role in sepsis development by regulating the glutathione, cysteamine, *PPAR* $\gamma$  and AKT signaling pathways. Further functional experiments might help us to clarify the role of *VNN1* in sepsis development.

Some potential limitations of the present study should be considered. First, the sample size of patients in each cohort was relatively small, which was remarkable in the discovery cohort. Additional large studies are needed to validate these findings. Second, we revealed that plasma vanin-1 levels were associated with traumatic sepsis. However, how vanin-1 affects the development of sepsis is unclear. More studies with cellular and molecular experiments are required to investigate the relevant mechanisms. Finally, although the correlations between plasma vanin-1 and traumatic sepsis were validated, whether the findings could be interpreted in other ethnic groups needs further evaluation.

## Conclusions

To summarize, our study demonstrated that plasma vanin-1 on admission is independently associated with the risk of traumatic sepsis and has a good predictive capacity to predict sepsis at the early stage of trauma. To confirm these findings, further studies with larger populations and functional evaluations are warranted.

## Abbreviations

APACHE II: Acute physiology and chronic health evaluation II; AUC: Area under the curve; CRP: C-reactive protein; ELISA: enzyme-linked immunosorbent assay; ISS: Injury severity score; PCT: Reciprocal; *PPAR* $\gamma$ : Peroxisome proliferator-activated receptor- $\gamma$ ; ROC: Receiver operating characteristic curve; SIRS: Systemic inflammatory response syndrome; SOFA: Sequential organ failure assessment.

## Declarations

### Ethics approval and consent to participate

The research was approved by the Institutional Ethics Review Board of the Army Medical University. Informed consent of all patients was obtained from the patients or their relatives.

### Consent for publication

Yes.

### Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author in response to reasonable requests.

### Competing interests

All authors have no competing interests to disclose.

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### Authors' contributions

W. Gu, A.Q. Zhang and J.X. Jiang designed the study. H.X. Lu and A.Q. Zhang were responsible for data collection and management. D.L. Wen, J. Du, D.Y. Du and J.H. Sun were responsible for sample collection and laboratory processing. H.X. Lu and L. Qiao performed statistical analysis and drafted the manuscript. W. Gu, A.Q. Zhang and J.X. Jiang critically revised the manuscript. All authors read and approved the final manuscript.

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## Figures

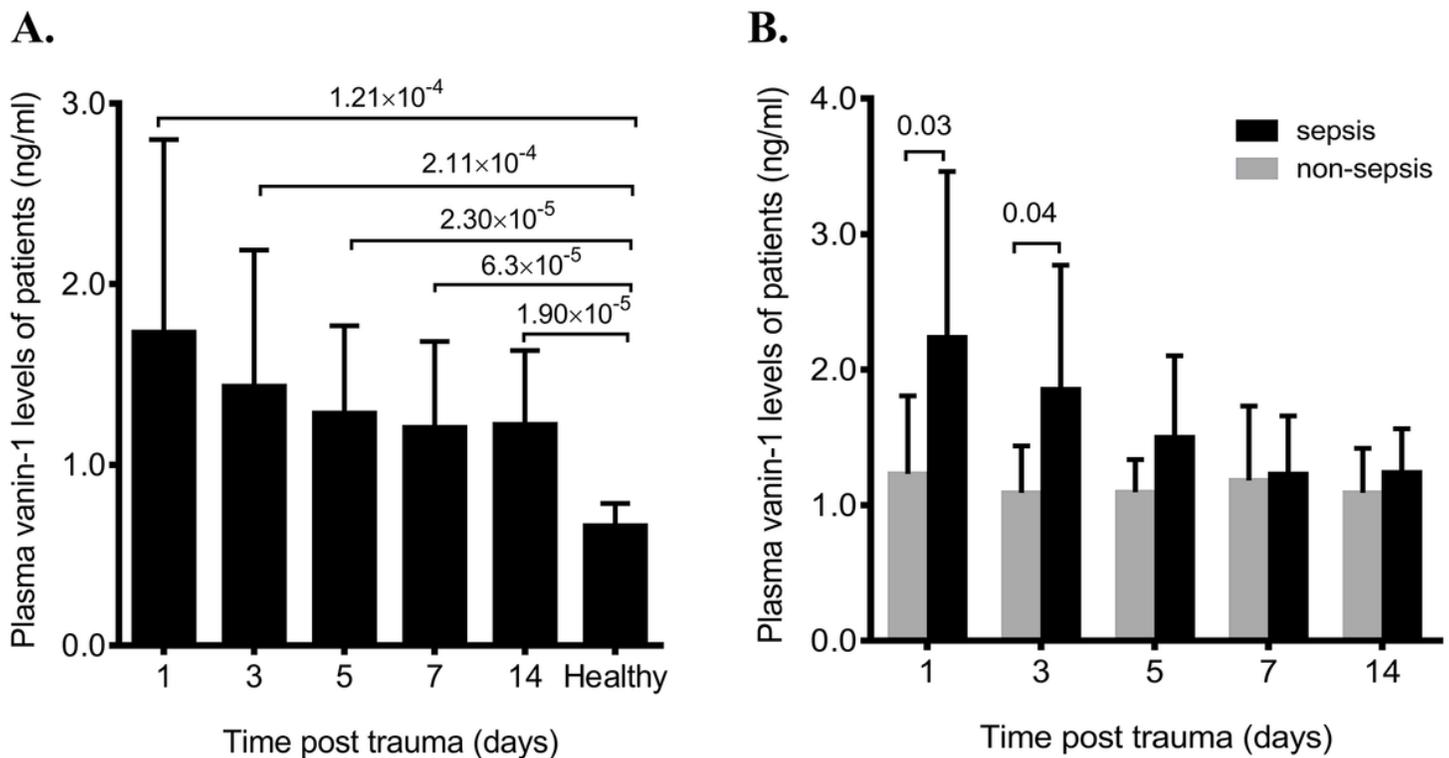


Figure 1

Kinetics of plasma vanin-1 levels in trauma patients on admission and at days 3, 5, 7, and 14 during hospitalization from the discovery cohort. A. Plasma vanin-1 of trauma patients is significantly higher than that of healthy volunteers (n=22 trauma patients vs. 16 healthy controls). B. Traumatic sepsis patients have higher plasma vanin-1 than non-sepsis patients on the early stage after injury (n=11 sepsis patients vs. 11 non-sepsis patients, P=0.03 for days 1 and P=0.04 for days 3). Data are expressed as the mean and 95% CI. Statistical analysis comprised Student's t test.

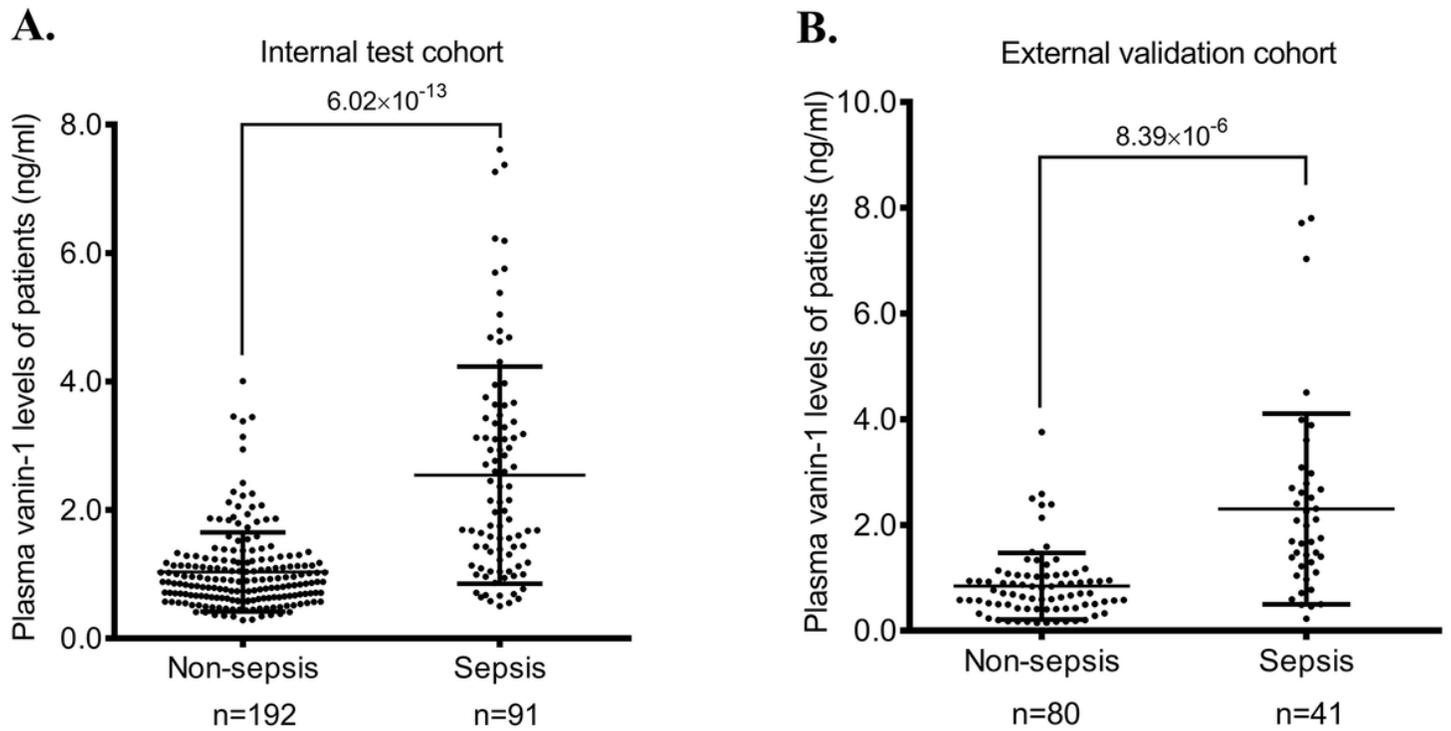
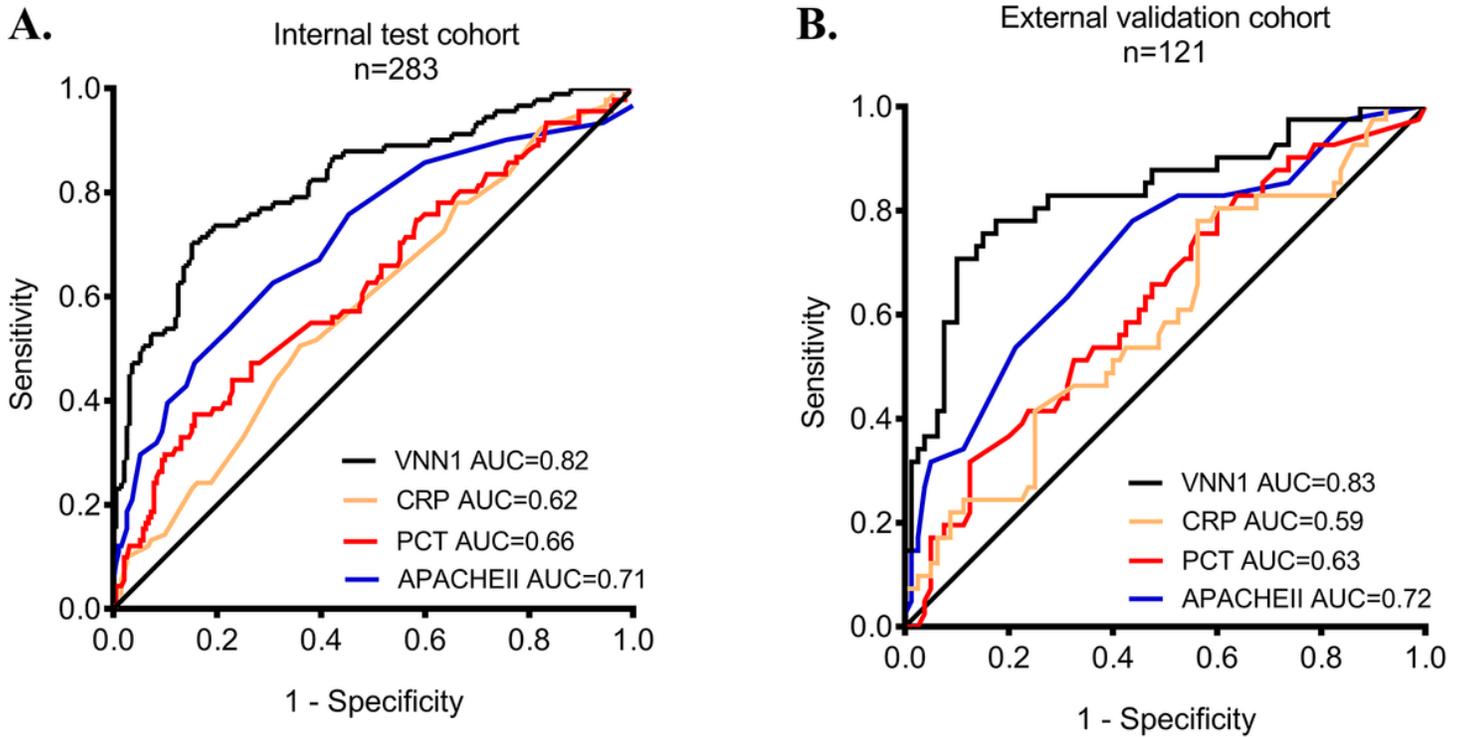


Figure 2

The plasma vanin-1 in trauma patients with and without sepsis for the internal test and external validation cohorts. Patients who developed sepsis had significantly higher levels of plasma vanin-1 when compared with patients who did not develop sepsis at day 1 after trauma (A for internal test cohort; B for external validation cohort). All samples were collected on day 1 after injury. Black bars show the mean and 95% CI. Statistical analysis comprised Student's t test.



**Figure 3**

Receiver operating curve (ROC) analysis of VNN1, CRP, PCT, and APACHE II for sepsis after trauma. Plasma vanin-1 obtained the best predictive value compared to other biomarkers and scores in the internal test cohort (A, n=283) and external validation cohort (B, n=121).

## Supplementary Files

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