Biomedical Research and Therapy 2024, 11(1):6151-6155

Open Access Full Text Article

Mini-Review

The diagnostic value of plasma gelsolin levels in sepsis: A mini review

Hussein A. Abid[1,2,*], Amirreza Jabbari[1], Hamid K. Al-Tameemi[3]

ABSTRACT

Sepsis remains a critical health concern with high mortality despite medical advances. Early diagnosis and risk stratification are vital to guide appropriate intervention and improve outcomes. Plasma gelsolin, an actin-binding protein that helps clear circulating filamentous actin, has emerged as a promising diagnostic and prognostic biomarker for sepsis. This review summarizes evidence on the usefulness of plasma gelsolin for these applications. Studies consistently show significantly decreased plasma gelsolin levels in septic humans and animal models compared to healthy controls. Reductions correlate with sepsis severity and development of multiorgan dysfunction. Plasma gelsolin demonstrates a potential to distinguish sepsis from non-infectious inflammation. It also aids in mortality prediction, with lower levels portending worse outcomes. One study found that sepsis non-survivors failed to recover depleted gelsolin levels over time, in contrast to survivors. The degree of gelsolin depletion is likely connected to the extent of cellular injury from sepsis, with consumption overwhelming plasma gelsolin's actin-scavenging capacity. Resulting persistent circulation of actin filaments is posited to mediate organ damage. Though most studies are limited by small sample sizes, plasma gelsolin consistently correlates with clinical deterioration. Substantiating its prognostic utility could enable risk stratification to guide sepsis management. Demonstrating a mortality benefit of gelsolin replacement therapy could also spur the development of novel treatments. Further research on plasma gelsolin is warranted to ultimately improve outcomes of this common and deadly syndrome.

Key words: biomarkers, diagnosis, gelsolin, sepsis, systemic inflammatory response syndrome

[1]*Department of Laboratory Diagnostics, Faculty of Health Sciences, University of Pécs, Pécs, Hungary*

[2]*Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Kadhimiya, Baghdad, Iraq*

[3]*Department of Medical Laboratory Technology, Bilad Alrafidain University College, Baqubah, Iraq*

Correspondence

Hussein A. Abid, Department of Laboratory Diagnostics, Faculty of Health Sciences, University of Pécs, Pécs, Hungary

Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Kadhimiya, Baghdad, Iraq

Email: mskc2d@pte.hu

History

- Received: Dec 19, 2023
- Accepted: Jan 28, 2024
- Published Online: Jan 31, 2024

DOI : 10.15419/bmrat.v11i1.859

INTRODUCTION

Sepsis remains a major cause of morbidity and mortality worldwide, with rising incidence and high in-hospital mortality [1,2]. Rapid detection of sepsis facilitates timely intervention, which is critical for improving patient outcomes [3]. However, the diagnosis can be challenging due to the heterogeneity of the clinical manifestations of sepsis [4]. Consequently, in this context, there is a great need for reliable diagnostic biomarkers to aid in the diagnosis of sepsis.

Actin is an abundant structural protein that makes up the cytoskeleton in most eukaryotic cells [5]. When cells are damaged or die due to injury or inflammation, actin is released into the extracellular space [6]. Free extracellular actin then undergoes polymerization to form long, insoluble filamentous actin (F-actin) [6,7]. These actin filaments can have detrimental effects systemically, including exacerbating vascular leakage, activating platelets, perturbing blood coagulation, and obstructing pulmonary microcirculation to impair gas exchange [8–11]. Moreover, circulating F-actin aggregates can trigger further inflammatory signaling when interacting with immune cells [12,13]. Together, these effects of extracellular F-actin propagate cellular damage and contribute to multiple organ dysfunction [14]. Plasma gelsolin (pGSN) plays a crucial role in mitigating these adverse effects of released actin [15]. As an actin-scavenging protein, pGSN binds and effectively removes circulating F-actin [15]. Thus, pGSN helps limit inflammatory and thrombotic complications of extensive cell injury and death.

During past two decades, pGSN has been an important and promising diagnostic markers for sepsis detection [16]. Previous studies have reported significantly decreased pGSN levels in patients with sepsis compared to non-septic patients or healthy controls [15,17–19]. The reductions appear to correlate with sepsis severity and development of multi-organ failure [20,21]. Furthermore, pGSN levels show diagnostic ability in distinguishing sepsis from non-infectious systemic inflammation [15,18,20,22]. Taken together, these findings indicate the potential usefulness of pGSN as a diagnostic biomarker for sepsis screening and as an indicator of sepsis severity. This mini review summarizes evidence on the diagnostic performance of pGSN specifically in sepsis and discuss its utility as a biomarker.

BioMedPress
The Open Access Publisher

Cite this article : Abid H A, Jabbari A, Al-Tameemi H K. **The diagnostic value of plasma gelsolin levels in sepsis: A mini review**. *Biomed. Res. Ther* 2024; 11(1):6151-6155.

GELSOLIN IN SEPSIS

Gelsolin was first described as an intracellular actin-binding protein that regulates cytoskeletal dynamics[23]. Its secreted isoform, pGSN, was later found to circulate in blood plasma at high levels and to serve a critical actin-scavenging function extracellularly[15]. The diagnostic potential of pGSN was recognized in the 1990s, when major tissue injury was shown to cause a rapid, profound drop in its levels[24]. A 1999 trauma study established decreased pGSN as an early prognostic biomarker that strongly predicts adverse outcomes like mortality[25]. Extensive research since has solidified the utility of pGSN as a biomarker reflecting the severity of cellular damage in various inflammation-driven conditions like sepsis, surgery, trauma, and critical illness[15,16,25,26]. The rapid decline in pGSN levels indicates overwhelmed actin-scavenging capacity and reflects a need for gelsolin repletion therapy, thereby making it a useful indicator of prognosis and a guide for potential therapeutic intervention.

STUDIES EVALUATING PGSN LEVELS IN SEPSIS

Several studies have evaluated pGSN levels in patients with sepsis. A study by Lee *et al.*[27] assessed plasma gelsolin levels in 21 non-surgical septic patients and found significantly decreased levels compared to healthy controls. Actin was detected in the plasma of 17/21 sepsis patients, suggesting that tissue injury and actin release occur early in sepsis. Septic non-survivors had significantly lower pGSN levels upon admission than survivors. The degree of pGSN depletion correlated with mortality risk, with every quartile reduction in pGSN associated with a 3.4-fold increase in the odds of death. Levels of pGSN were more predictive of the outcome than were APACHE III scores.

Another study by Wang *et al.*[20] measured pGSN levels in 91 surgical ICU patients with severe sepsis. Levels were significantly decreased compared to both non-septic ICU patients and healthy controls. An inverse correlation was found between pGSN levels upon admission and APACHE II scores. Although pGSN levels upon admission did not differ between sepsis survivors and non-survivors, only survivors exhibited recovery of depleted pGSN levels over time.

Huang *et al.*[28] evaluated 102 burn patients, 43 of whom developed sepsis. Levels of pGSN decreased with increasing burn size and were significantly lower in septic than non-septic patients at multiple timepoints. Sepsis non-survivors had lower pGSN levels than survivors. Logistic regression found that pGSN levels were inversely associated with sepsis occurrence and sepsis mortality.

A pilot study by Halis *et al.* also measured pGSN levels in 40 preterm infants with neonatal sepsis[18]. Gelsolin levels were significantly lower during sepsis compared to after recovery and in healthy controls. Gelsolin levels also were inversely correlated with clinical sepsis scores. The authors proposed that gelsolin may be a valuable biomarker for neonatal sepsis.

DIAGNOSTIC ACCURACY OF GELSOLIN FOR SEPSIS

A few studies have examined the potential diagnostic accuracy of using pGSN levels to identify sepsis patients. Lee *et al.*[27] performed receiver operating characteristic (ROC) analysis, which showed moderate predictive ability of pGSN levels for 28-day mortality in sepsis patients, with an area under the curve (AUC) of 0.86. Using a cutoff of 113.6 mg/l, pGSN had 66.7% sensitivity and 93.3% specificity for mortality prediction. The AUC was slightly higher compared to that of APACHE III scores. This indicates that pGSN levels have reasonable accuracy for distinguishing sepsis survivors from non-survivors.

In addition, the study of Halis *et al.*[18] had also assessed the diagnostic value of gelsolin through ROC curve analysis which showed strong predictive ability, with an AUC of 0.96 when using pGSN levels to diagnose sepsis. Sensitivity was 90.3% and specificity 95% using a cutoff of 44.97 μg/ml.

The utility of serum gelsolin for differentiating sepsis from non-infectious systemic inflammation was evaluated by Horváth-Szalai *et al.*[22] as well. Gelsolin demonstrated an AUC of 0.77 for distinguishing sepsis from SIRS patients ($p < 0.05$). The optimal cut-off value was determined to be 21.04 mg/L, resulting in a sensitivity of 83.3% and a specificity of 68.7% for diagnosing sepsis. Furthermore, for predicting 7-day mortality in the sepsis cohort, gelsolin had an AUC of 0.74 ($p < 0.05$). A gelsolin level below 11.38 mg/L predicted mortality with 76.2% sensitivity and 72.7% specificity. Their findings suggested that gelsolin demonstrated diagnostic and prognostic utility in this sepsis study, distinguishing it from non-infectious SIRS and predicting short-term mortality with moderate accuracy comparable to established biomarkers like procalcitonin[22].

CORRELATION OF GELSOLIN LEVELS WITH OUTCOMES

Multiple studies have shown an association between decreased pGSN levels and poor outcomes in critically ill patients. In a study of 91 patients with severe

sepsis, non-survivors failed to recover their depleted gelsolin levels over time, whereas survivors showed substantial recovery of gelsolin levels starting around day 11 [20]. Another study of burn patients found significantly lower gelsolin levels in those who developed and died from sepsis compared to those without sepsis and survivors of sepsis [29]. Lower gelsolin levels upon admission have also been correlated with increased mortality after major trauma and in surgical ICU patients [18,25–27]. The mechanism likely involves extensive actin exposure from cellular injury that consumes circulating gelsolin. Loss of gelsolin's ability to clear actin and bind inflammatory mediators then leads to exacerbation of inflammation and tissue damage. The correlation of gelsolin recovery with clinical improvement supports its pathogenetic role.

CURRENT LIMITATIONS

While existing evidence consistently links low pGSN levels with worse outcomes, most studies to date have been small pilot investigations. Larger, multicenter trials are needed to definitively establish gelsolin as a prognostic biomarker for critical illness. There has also been heterogeneity in study populations and gelsolin measurement methodology among studies. Establishing standard reference ranges and optimal methods for determining gelsolin levels will help facilitate broader clinical adoption. More research is also needed to clarify the mechanisms connecting gelsolin depletion to organ injury in sepsis and related inflammatory states. Finally, though animal studies showing a mortality benefit of gelsolin replacement are promising, further investigation of therapeutic potential in human sepsis is needed.

POTENTIAL CLINICAL AND RESEARCH IMPLICATIONS

If substantiated as an early prognostic indicator of severity and mortality risk of sepsis, pGSN testing could aid in risk stratification and decision making for critically ill patients. Low gelsolin upon admission may warrant more aggressive resuscitation, while failure to recover pGSN levels could indicate poor prognosis. In a research setting, pGSN levels may aid in patient selection and serve as a surrogate endpoint for clinical trials investigating new sepsis treatments. Demonstrating the efficacy of gelsolin repletion therapy in human sepsis could also spur development of gelsolin-based drugs to improve outcomes. Research efforts focused on illuminating gelsolin's protective mechanisms against organ dysfunction may uncover novel therapeutic targets. Thus, pGSN has promise both as a clinical prognostic tool and as a facilitator of further research to enhance our approach for managing sepsis.

CONCLUSIONS

In conclusion, existing evidence suggests that pGSN, as an actin-scavenging protein that helps mitigate cellular injury from inflammation, has potential utility as both a diagnostic and prognostic biomarker for sepsis. Multiple studies have shown significant reductions in pGSN levels during sepsis compared to a healthy state. The degree of depletion correlates with sepsis severity and development of organ dysfunction, while failure of gelsolin levels to recover portends worse outcomes. Though larger studies are needed to confirm these findings and establish standard reference values, current data indicate that pGSN testing could aid in clinical decision-making for sepsis patients. Low or falling levels may prompt earlier intervention or predict mortality risk. If gelsolin's protective role is further validated, repletion therapy could also emerge as a novel sepsis treatment. Thus, continued research on pGSN in sepsis is warranted and may ultimately help transform management of this deadly syndrome. Understanding the mechanisms linking gelsolin to inflammation and tissue damage could uncover new therapeutic targets, as well. In summary, as a window into systemic inflammatory burden and tissue injury, pGSN shows promise both for guiding clinical care and facilitating translational research to improve sepsis outcomes.

ABBREVIATIONS

pGSN: plasma gelsolin, **SIRS**: systemic inflammatory response syndrome

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

H.A.A conceived the concept. H.A.A and A.J wrote the manuscript. H.K.A-T critically revised the manuscript. All authors have read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

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

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Salomão R, Ferreira BL, Salomão MC, Santos SS, Azevedo LC, Brunialti MK. Sepsis: evolving concepts and challenges. Brazilian Journal of Medical and Biological Research. 2019;52(4):e8595. PMID: 30994733. Available from: https://doi.org/10.1590/1414-431x20198595.
2. Heming N, Azabou E, Cazaumayou X, Moine P, Annane D. Sepsis in the critically ill patient: current and emerging management strategies. Expert Review of Anti-Infective Therapy. 2021;19(5):635–47. PMID: 33140679. Available from: https://doi.org/10.1080/14787210.2021.1846522.
3. Kim HI, Park S. Il, Park S. Sepsis: early recognition and optimized treatment. Tuberculosis and Respiratory Diseases. 2019;82(1):6–14. PMID: 30302954. Available from: https://doi.org/10.4046/trd.2018.0041.
4. Pant A, Mackraj I, Govender T. Advances in sepsis diagnosis and management: a paradigm shift towards nanotechnology. Journal of Biomedical Science. 2021;28(1):6. PMID: 33413364. Available from: https://doi.org/10.1186/s12929-020-00702-6.
5. Beaulieu V, Silva ND, Pastor-Soler N, Brown CR, Smith PJ, Brown D. Modulation of the actin cytoskeleton via gelsolin regulates vacuolar H+-ATPase recycling. The Journal of Biological Chemistry. 2005;280(9):8452–63. PMID: 15591047. Available from: https://doi.org/10.1074/jbc.M412750200.
6. Grzanka D, Gagat M, Izdebska M. Actin is required for cellular death. Acta Histochemica. 2013;115(8):775–82. PMID: 23683404. Available from: https://doi.org/10.1016/j.acthis.2013.04.002.
7. Janmey PA, Hvidt S, Oster GF, Lamb J, Stossel TP, Hartwig JH. Effect of ATP on actin filament stiffness. Nature. 1990;347(6288):95–9. PMID: 2168523. Available from: https://doi.org/10.1038/347095a0.
8. Lappalainen P, Kotila T, Jégou A, Romet-Lemonne G. Biochemical and mechanical regulation of actin dynamics. Nature Reviews Molecular Cell Biology. 2022;23(12):836–52. PMID: 35918536. Available from: https://doi.org/10.1038/s41580-022-00508-4.
9. Weise-Cross L, Sands MA, Sheak JR, Broughton BR, Snow JB, Bosc LVG. Actin polymerization contributes to enhanced pulmonary vasoconstrictor reactivity after chronic hypoxia. American Journal of Physiology Heart and Circulatory Physiology. 2018;314(5):1011–21. PMID: 29373038. Available from: https://doi.org/10.1152/ajpheart.00664.2017.
10. White JG. Arrangements of actin filaments in the cytoskeleton of human platelets. American Journal of Pathology. 1984;117(2):207–17. PMID: 6149688.
11. Du L, Zhou J, Zhang J, Yan M, Gong L, Liu X. Actin filament reorganization is a key step in lung inflammation induced by systemic inflammatory response syndrome. American Journal of Respiratory Cell and Molecular Biology. 2012;47(5):597–603. PMID: 22721831. Available from: https://doi.org/10.1165/rcmb.2012-0094OC.
12. Valensin S, Paccani SR, Ulivieri C, Mercati D, Pacini S, Patrussi L. F-actin dynamics control segregation of the TCR signaling cascade to clustered lipid rafts. European Journal of Immunology. 2002;32(2):435–46. PMID: 11813162. Available from: https://doi.org/10.1002/1521-4141(200202)32:2<435:AID-IMMU435>3.0.CO;2-H.
13. Colin A, Bonnemay L, Gayrard C, Gautier J, Gueroui Z. Triggering signaling pathways using F-actin self-organization. Scientific Reports. 2016;6(1):34657. PMID: 27698406. Available from: https://doi.org/10.1038/srep34657.
14. Sudakov NP, Klimenkov IV, Byvaltsev VA, Nikiforov SB, Konstantinov YM. Extracellular actin in health and disease. Biochemistry (Moscow). 2017;82(1):1–12. PMID: 28320282. Available from: https://doi.org/10.1134/S0006297917010011.
15. Piktel E, Levental I, Durnaś B, Janmey PA, Bucki R. Plasma gelsolin: indicator of inflammation and its potential as a diagnostic tool and therapeutic target. International Journal of Molecular Sciences. 2018;19(9):2516. PMID: 30149613. Available from: https://doi.org/10.3390/ijms19092516.
16. Ragán D, Kustán P, Horváth-Szalai Z, Szirmay B, Miseta A, Woth G. Presepsin: gelsolin ratio, as a promising marker of sepsis-related organ dysfunction: a prospective observational study. Frontiers in Medicine. 2023;10:1126982. PMID: 37215727. Available from: https://doi.org/10.3389/fmed.2023.1126982.
17. Horváth-Szalai Z, Kustán P, Szirmay B, Lakatos A, Christensen PH, Huber T. Validation of an automated immune turbidimetric assay for serum gelsolin and its possible clinical utility in sepsis. Journal of Clinical Laboratory Analysis. 2018;32(3):e22321. PMID: 28872708. Available from: https://doi.org/10.1002/jcla.22321.
18. Halis H, Gunes T, Korkut S, Saraymen B, Sen A, Bastug O, et al. In the diagnosis of neonatal sepsis importance of gelsolin and relationship with mortality and morbidity. Medical Hypotheses. 2016;94:77–80. PMID: 27515207. Available from: https://doi.org/10.1016/j.mehy.2016.06.017.
19. El-Maghraby A, Mowafy H, Omer E, El-Akabawy H, Nessim I. Diagnostic and prognostic value of plasma gelsolin in multi-organ failure in patients with sepsis. Open Access Macedonian Journal of Medical Sciences. 2021;9(B):29–35. Available from: https://doi.org/10.3889/oamjms.2021.5281.
20. Wang H, Cheng B, Chen Q, Wu S, Lv C, Xie G. Time course of plasma gelsolin concentrations during severe sepsis in critically ill surgical patients. Critical Care (London, England). 2008;12(4):106. PMID: 18706105. Available from: https://doi.org/10.1186/cc6988.
21. Huang LF, Yao YM, Li JF, Dong N, Liu C, Yu Y, et al. Reduction of plasma gelsolin levels correlates with development of multiple organ dysfunction syndrome and fatal outcome in burn patients. PloS one. 2011;6(11):e25748. Available from: https://doi.org/10.1371/journal.pone.0025748.
22. Horváth-Szalai Z, Kustán P, Mühl D, Ludány A, Bugyi B, Koszegi T. Antagonistic sepsis markers: serum gelsolin and actin/gelsolin ratio. Clinical Biochemistry. 2017;50(3):127–33. PMID: 27823961. Available from: https://doi.org/10.1016/j.clinbiochem.2016.10.018.
23. DiNubile MJ. Plasma gelsolin as a biomarker of inflammation. Arthritis Research & Therapy. 2008;10(6):124. PMID: 19105851. Available from: https://doi.org/10.1186/ar2547.
24. Lee WM, Galbraith RM, Galbraith RM. The extracellular actin-scavenger system and actin toxicity. The New England Journal of Medicine. 1992;326(20):1335–41. PMID: 1314333. Available from: https://doi.org/10.1056/NEJM199205143262006.
25. Mounzer KC, Moncure M, Smith YR, Dinubile MJ. Relationship of admission plasma gelsolin levels to clinical outcomes in patients after major trauma. American Journal of Respiratory and Critical Care Medicine. 1999;160(5 Pt 1):1673–81. PMID: 10556139. Available from: https://doi.org/10.1164/ajrccm.160.5.9807137.
26. Lee PS, Drager LR, Stossel TP, Moore FD, Rogers SO. Relationship of plasma gelsolin levels to outcomes in critically ill surgical patients. Annals of Surgery. 2006;243(3):399–403. PMID: 16495706. Available from: https://doi.org/10.1097/01.sla.0000201798.77133.55.
27. Lee PS, Patel SR, Christiani DC, Bajwa E, Stossel TP, Waxman AB. Plasma gelsolin depletion and circulating actin in sepsis—A

pilot study. PloS one. 2008;3(11):e3712. Available from: https://doi.org/10.1371/journal.pone.0003712.

28. Huang LF, Yao YM, Dong N, He LX, Zhang QH, Yu Y, et al. Plasma gelsolin level and its relationship with the prognosis of patients with severe burns. Chinese Journal of Burns. 2013;29(2):148–51. Available from: https://doi.org/10.3760/cma.j.issn.1009-2587.2013.02.014.
29. Xianhui L, Pinglian L, Xiaojuan W, Wei C, Yong Y, Feng R. The association between plasma gelsolin level and prognosis of burn patients. Burns. 2014;40(8):1552–5. PMID: 24690274. Available from: https://doi.org/10.1016/j.burns.2014.02.020.