Prevalence of severe thrombocytopenia in sepsis

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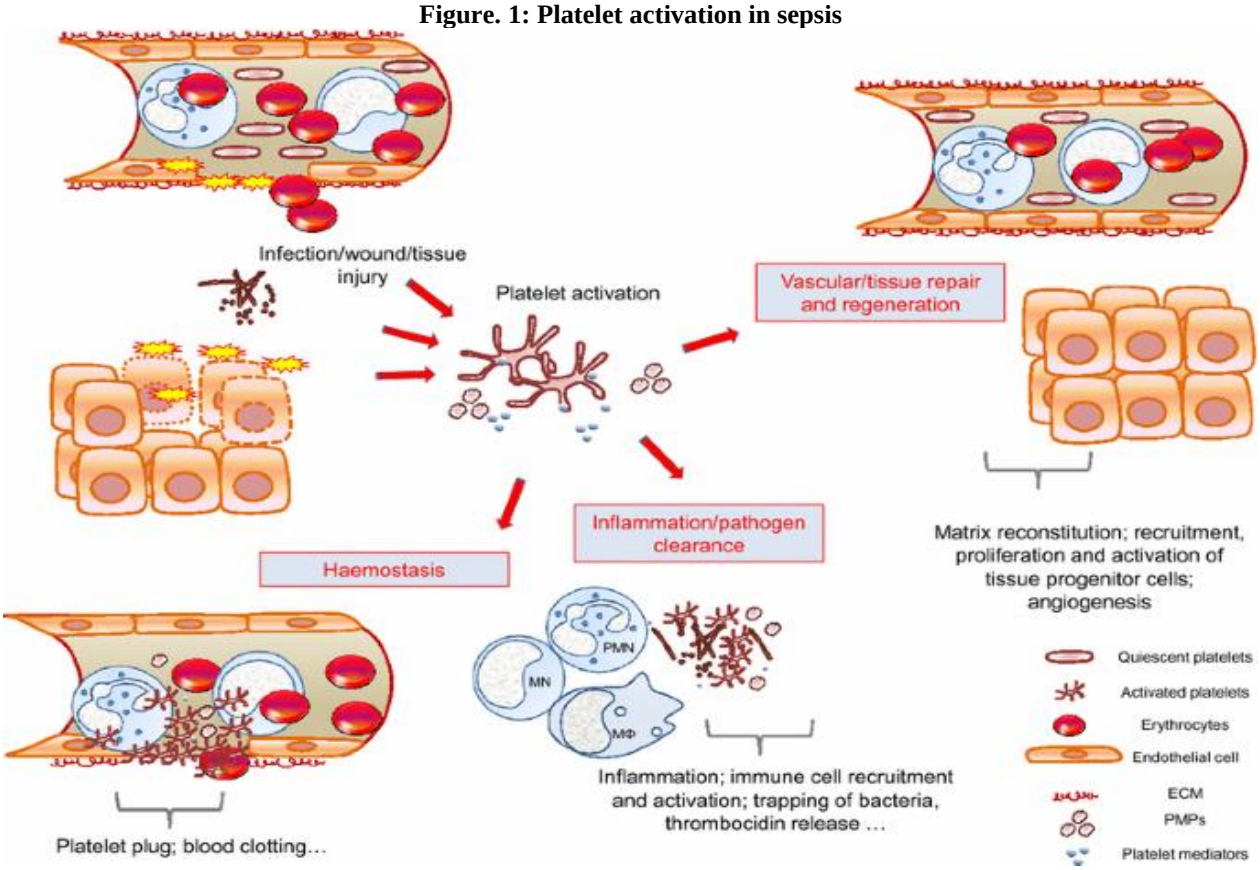
***Abstract*- First, platelet count changes are common in the intensive care unit (ICU). Using common thresholds for platelet count, thrombocytopenia accounts for 20-50% of all critical care patients.**
Aim of the study is to identify the prevalence of severe thrombocytopenia in sepsis.
Methodology- Prospective cross-sectional study.
Result and conclusion: Prevalence of thrombocytopenia in sepsis was 34%

***Index Terms*- Thrombocytopenia, sepsis, immune response.**

INTRODUCTION

Platelets harbor different mediators that are stored in morphologically distinct pools of granules. The cataloging of platelet-derived mediators reflects the striking diversity of platelets in hemostasis, thrombosis, and immune responses.
The secretion of granule contents after platelet activation by agonists is central to platelet function.
Platelet activation induces membrane protein expression and mediator release through multiple mechanisms. Activated platelets also release vesicles containing platelet microparticles (PMPs) and exosomes. Platelets are the major source of circulating MPs. Several agonists are produced in pathological conditions associated with platelet activation.
Platelets encounter inhibitory signals such as nitric oxide and prostacyclin released by endothelial cells (ECs) that prevent their activation in healthy blood vessels. Platelets circulate in close proximity to the vessel wall, and disruption of the EC lining overcomes inhibitory signals and promotes platelet adhesion, activation, and aggregation, resulting in temporary occlusion of injured vessels.
Platelets not only bind to damaged blood vessels to prevent bleeding, but also support a range of recently studied functions that may be reflected in the diversity of platelet mediators. Platelets are activated under conditions that disrupt tissue homeostasis and directly and indirectly regulate various stages of inflammation, contributing to pathogen clearance, wound healing, and tissue regeneration (Figures 1, 2).). As such, platelets are now recognized as an essential component of the innate immune response, monitoring harmful signals and responding rapidly.

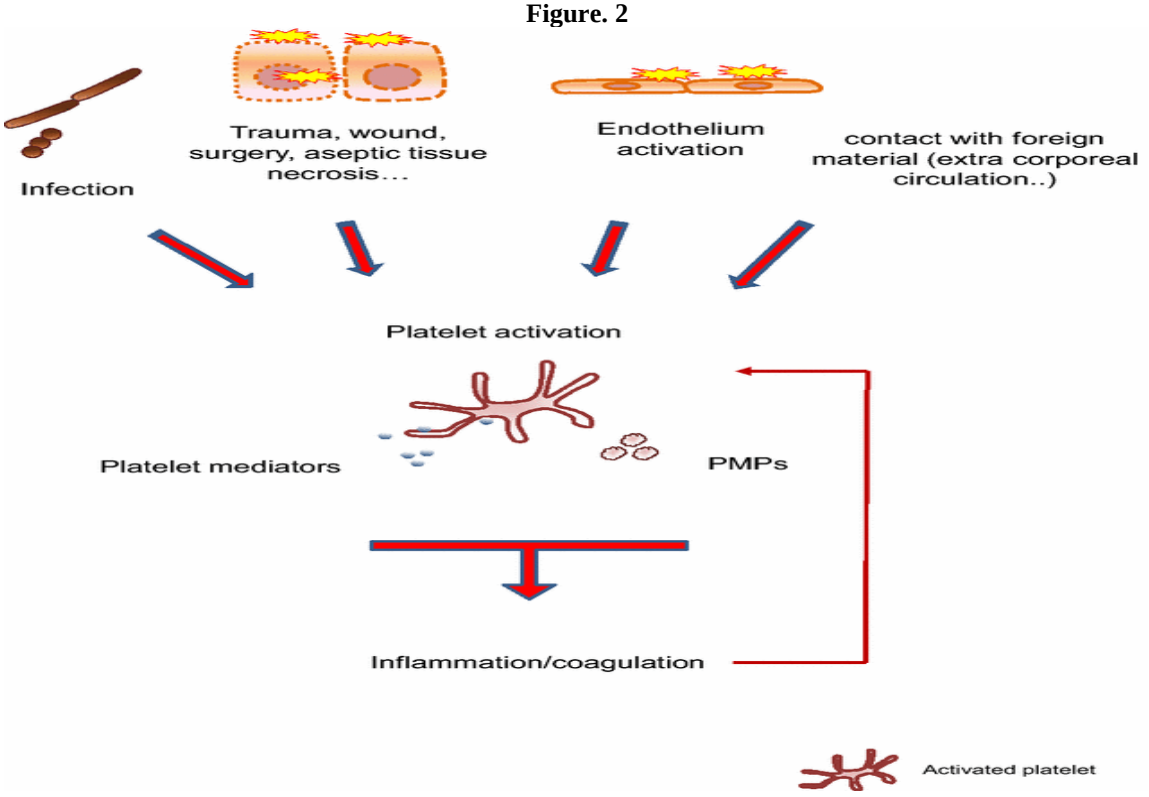
Figure. 1: Platelet activation in sepsis



Platelets play an important role in immune responses associated with hemostasis, thrombosis, inflammation, pathogen clearance, and tissue repair.

There is increasing evidence emphasizing a role for platelets other than hemostasis and thrombosis. Some of the platelet interfaces in the innate immune response are schematized. Platelets are activated at sites of infection/tissue damage. Platelets and platelet-derived mediators stop bleeding, eliminate pathogens directly or indirectly by acting on different stages of the immune response, and strengthen blood vessels/tissues by providing matrix components and various signals. Promotes repair, remodels matrix and attracts tissue progenitor cells. Remodeling of the vascular framework. Platelets provide a coherent biological response that helps heal infections and restore tissue architecture and homeostasis. Platelet-derived microparticles (PMPs) recapitulate some activated platelet functions. ECM extracellular matrix, MN monocytes, PMN polymorphonuclear neutrophils, MΦ macrophages

Figure. 2



Platelets sense and activate several signals generated in dangerous situations to which the organism is exposed. Interactions with pathogens, endothelial cell/tissue damage, and interactions with foreign substances activate platelets (see text for details). Platelet activation triggers a variety of responses, including activation of various inflammatory and coagulation pathways. Inflammatory and coagulation signals activate platelets (thin arrows). PMPs platelet microparticles.

Platelets as key players in the inflammatory response. Important link with clotting

Activated platelets abundantly secrete pro-inflammatory substances, cytokines/chemokines, vasoactive amines, eicosanoids, and components of proteolytic cascades that directly or indirectly promote inflammation through the activation of surrounding target cells. increase. When stimulated by inflammatory mediators, ECs undergo profound changes collectively termed 'EC activation', resulting in cell adhesion molecule and tissue factor expression, von Willebrand factor, cytokines/chemokines, proteases, and nitrate levels. produce production. Platelets adhere to activated ECs through a multistep process in which glycans play a key role.

Inflammation may also alter the protective EC glycocalyx barrier and promote platelet adhesion. Platelet activation during inflammation alters vascular tone, increases vascular barrier permeability and contributes to the generation of cytopathic signals such as: B. Mediates the generation of reactive oxygen species by neutrophils, thereby affecting the vasculature. Leukocytes are her second important target of platelets, and platelet/leukocyte interactions are essential for inflammation.

Platelet/leukocyte interactions are key steps in leukocyte recruitment, activation, and migration in inflammation. Moreover, upon interaction, platelets activate neutrophils and monocytes through multiple mechanisms, including triggering TREM-1 on neutrophils, leading to various pro-inflammatory responses. Platelet/leukocyte aggregate formation in the blood is dependent on platelet activation and is an early event in the progression of sepsis. For example, the platelet/neutrophil complex increases in early stages but decreases in complicated sepsis. This may reflect peripheral sequestration or sepsis-associated thrombocytopenia, in which administration of endotoxin in humans leads to an increase followed by a brief decrease in circulating platelet/neutrophil aggregates.

Increased inflammation results from the reciprocal activation between platelets and their target cells, and circulating monocyte/and neutrophil/platelet aggregates may contribute to the propagation of inflammatory signals. Importantly, it also helps control and resolve inflammation through multiple mechanisms, such as the release of anti-inflammatory cytokines and inflammatory mediators. It has both procoagulant properties.

Proinflammatory cytokines released by platelets can also activate the coagulation cascade at various stages. Conversely, activation of blood coagulation by platelets generates various inflammatory effectors such as thrombin. In addition, inflammatory mediators

may impair the mechanisms of anticoagulant and fibrinolytic signaling pathways and contribute to coagulation dysregulation in sepsis.

Therefore, platelet inflammatory mediators may contribute to septic coagulopathy. PMPs retain many of the proinflammatory and procoagulant properties of parent platelets and are thought to diffuse inflammatory and coagulation signals.

AIM OF THE STUDY

To study the prevalence of severe thrombocytopenia in sepsis

MATERIALS AND METHOD

PATIENT SELECTION

All patients in Medicine IPD/ ICU medical histories and laboratory findings were taken up for the study. Based on confidence level 95%, margin of error 5%, Population proportion of 50%, and population size 100, the calculated sample size is 80.

SAMPLING TECHNIQUE

Consecutive sampling

STUDY DESIGN

Prospective Cross sectional study

STUDY SETTING

----------Medical college

STUDY PERIOD

November 2021- October 2022

RESULTS

Among the study participants, 43% were males and 57 % were females.

Figure 3: Gender of study participants

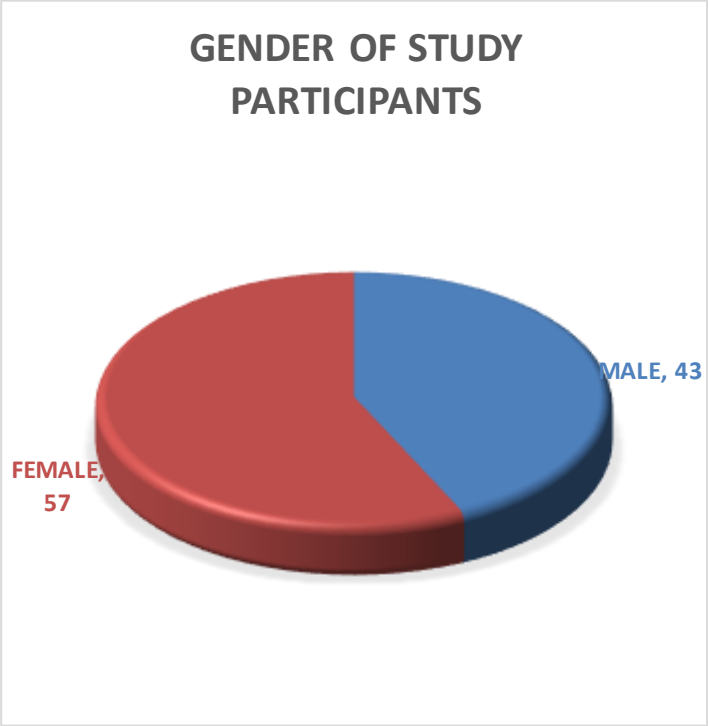
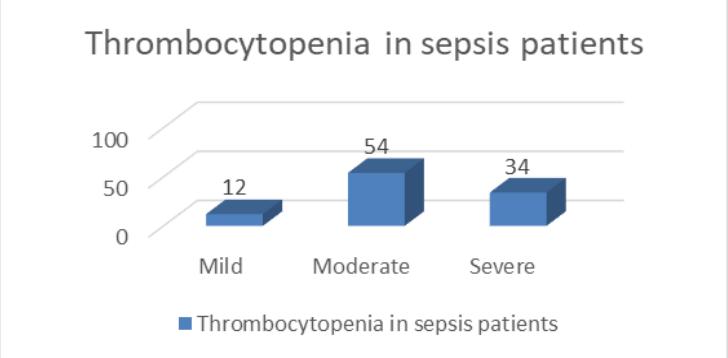
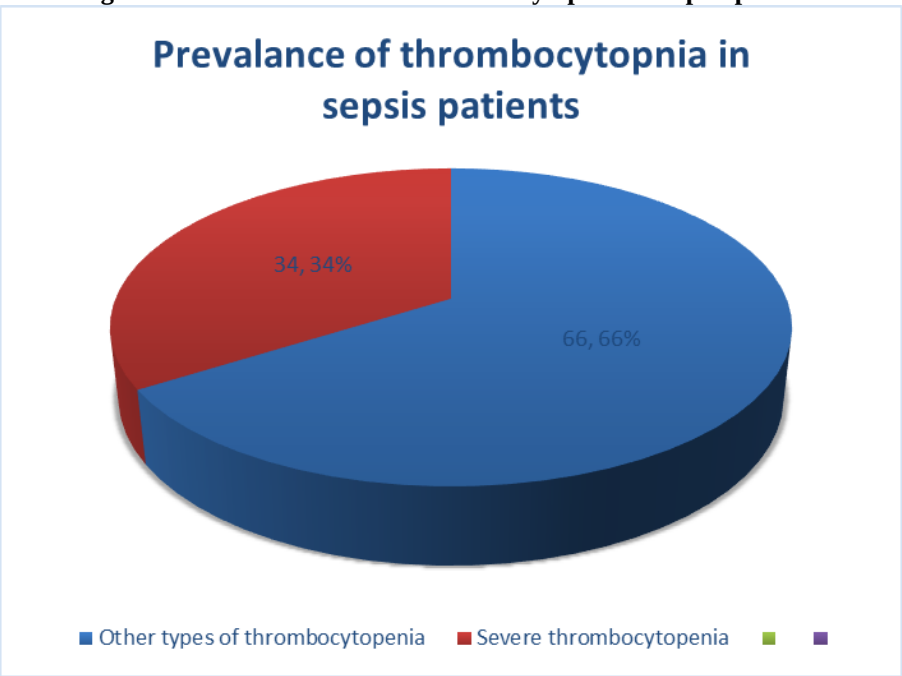


Figure 4: Thrombocytopenia in sepsis patients



Out of 80 patients who were on treatment with sepsis, 12 had mild thrombocytopenia, 54 had moderate thrombocytopenia and 34 had severe thrombocytopenia.

Figure 5: Prevalence of severe thrombocytopenia in sepsis patients



This study depicts that 34% of the study participants had severe sepsis among the patients who were admitted for sepsis treatment due to various organic causes leading on to DIC.

DISCUSSION

Coagulation disorders contribute to the SOFA score for organ damage in sepsis, and circulating platelet counts are used to assess. The incidence of thrombocytopenia is particularly high in patients with sepsis, and the degree of thrombocytopenia is a marker of poor prognosis associated with increased bleeding risk, increased organ dysfunction and, in some cases, increased 28-day mortality. Several mechanisms may contribute to the severe thrombocytopenia that occurs late in the clinical course of sepsis. Therefore, it is important to understand the multiple molecular mechanisms underlying thrombocytopenia in order to elucidate the role of platelets and identify biomarkers of platelet function that emerge early in the clinical course of sepsis. A recent systematic review concluded that increased circulating immature platelets are associated with severe sepsis and increased mortality. Platelets adhere and aggregate to the activated endothelium, providing a procoagulant membrane surface for the formation of additional fibrin clots in DIC. Platelet aggregates are observed in the organ microvasculature of models of LPS-induced sepsis and polymicrobial sepsis.

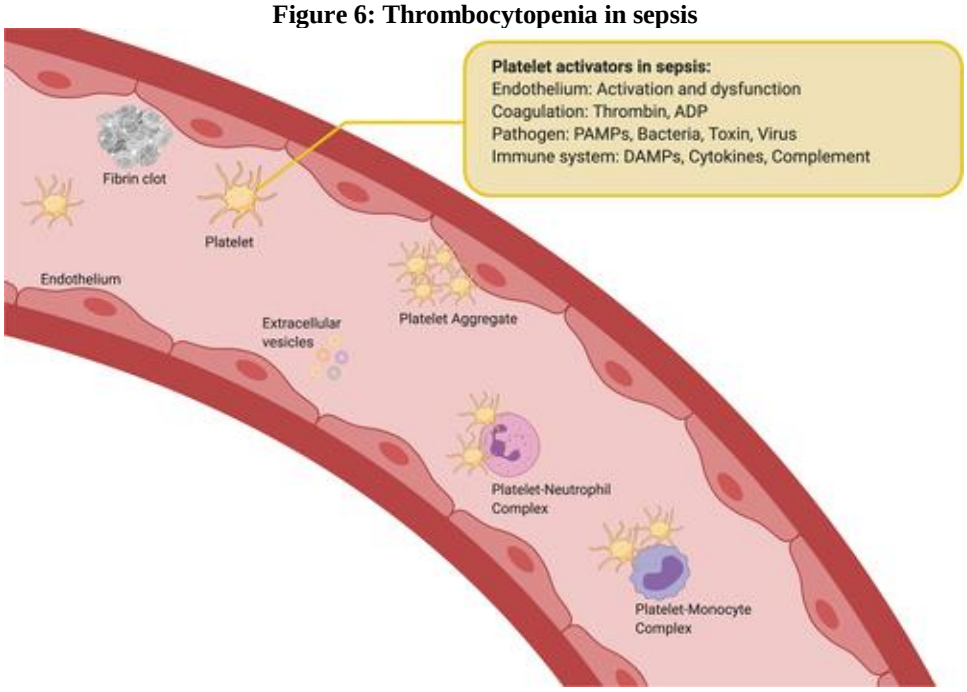
Platelet thrombi are present in hepatic microvessels and are associated with increased organ dysfunction in polymicrobial and streptococcal sepsis models. Increased platelet activation has been reported in patients with sepsis, but sample sizes in these studies are often relatively small.

Ex vivo platelet populations show increased surface-bound thrombospondin and platelet-leukocyte complex formation, correlating with organ dysfunction. Platelet aggregation decreased in response to ex vivo stimulation, indicating that platelet activation occurred in vivo. Upregulation of P-selectin on the activated platelet surface and formation of platelet-monocyte complexes were higher in patients with Gram-positive sepsis than in those with Gram-negative sepsis, suggesting that different platelet phenotypes are associated with different pathogens. suggesting that they are related.

Platelets are innate immune cells that elaborate an impressive immune receptor repertoire for recognizing inflammatory mediators, injury-associated molecular patterns, PAMPs, and leukocytes. Platelets regulate endothelial and leukocyte function through direct receptor-mediated contact, extracellular vesicle release, and cytokine and chemokine release.

The contribution of platelets to immune responses to bacterial, malaria, and viral infections has been extensively reviewed elsewhere. During coronavirus disease 2019 (COVID-19) discussed in Koupenova, platelets play an increasingly important role in the immune response. to increase.

Figure 6: Thrombocytopenia in sepsis



Platelets can be rapidly activated in sepsis by either pathogens, components of the activated coagulation system, or immune mediators. Activated platelets release granule proteins and extracellular vesicles (EVs) that have immunomodulatory effects on endothelial cells and leukocytes. When activated, platelets form heterotypic complexes with neutrophils or monocytes, directly affecting immune cell function. First, they reported that platelets directly bind bacteria and become trapped in platelet-bacteria aggregates.

Platelet activation and aggregation are now known to occur in response to many Gram-positive bacteria. Importantly, multiple platelet receptors can be targeted directly by various bacterial proteins or indirectly through plasma protein cross-linking. Recently, a common mechanism of platelet activation was reported for the major human pathogens Staphylococcus aureus and Streptococcus pneumoniae. M protein released from Streptococcus pyogenes forms a complex with plasma fibrinogen and IgG attacks platelet GPIIb/IIIa and FcγRIIA receptors to mediate platelet activation. The absence of her FcγRIIA receptor on mouse platelets presents a major challenge when studying interactions between these platelets and bacteria in experimental models of sepsis. Importantly, transgenic FcγRIIA mice have been generated and against this background it is highly informative to study bacterial sepsis and organ dysfunction. A recent study used FcγRIIA transgenic mice to demonstrate a dominant role for this receptor in immune complex-mediated thrombocytopenia and platelet sequestration in a mouse model of systemic inflammation. Taken together, these studies demonstrate that platelet activation and degranulation can follow thrombocytopenia, and for other bacteria and bacterial factors in experimental in vivo models of E. coli and S. aureus. also shows. We will investigate this phenomenon further. S. pyogenes is killed by platelet bacterial aggregates formed in vitro, and after platelet activation upon platelet depletion, advanced interactions between S. pyogenes and complement C3 and tissue-resident immune cells in the spleen and liver. Collaboration takes place. it's not. Taken together, these studies demonstrate that platelets exert multiple bactericidal effects that contribute to immune defense. nHuman and mouse platelets express a functional Toll-like receptor 4 on their surface. Traditional features of platelet activation, including P-selectin expression and platelet aggregation, are not observed in response to LPS. Importantly, potent platelet-dependent tumor necrosis factor production is induced by LPS administration to mice.

GPVI and C-type lectin receptor (CLEC-2) are major immunoreceptors and receptors with tyrosine-based activation motifs expressed on both human and mouse platelets. Recent studies have described the role of these receptors in inflammation and sepsis. In mouse models of pulmonary sepsis, GVI, but not CLEC-2, is essential for maintaining local pulmonary immunity. Mice lacking functional GPVI exhibit an increased bacterial burden at the site of infection and decreased platelet-leukocyte complex formation. CLEC-2 contributes to thrombosis and organ damage in mouse models of systemic Salmonella typhimurium infection. A recent study suggested that CLEC-2 has an important immunomodulatory role in his two mouse models of LPS- or CLP-induced sepsis. Her CLEC-2 exposure via podoplanin modulates immune cell recruitment and cytokine-driven inflammation, preventing organ damage in both models. Neutrophils and monocytes are key cell organizers of the innate immune response and are pathologically dysregulated in sepsis. Activated platelets form complexes with neutrophils (PNC) and monocytes (PMC), with subsequent crosstalk leading to regulation of leukocyte function. The figure summarizes the immunomodulatory effects of platelets on neutrophil and monocyte function in the context of sepsis.

CONCLUSION

This study shows the prevalence of severe thrombocytopenia in patients with sepsis is 34%.

RECOMMENDATION

The study should be done among more no. of patients at different settings to identify the trend of the thrombocytopenia in sepsis.

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