REVIEW

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The Potential Clinical Relevance of Procoagulant Microparticles as Biomarkers of Blood Coagulation in Breast Cancer: A Systematic Review

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Abstract

Background: Breast cancer (BC) is a global challenge that affects a large portion of individuals, especially women. It has been suggested that microparticles (MPs) can be used as a diagnostic, prognostic, or therapeutic biomarker in various diseases. Moreover, MPs are known to elevate in cancer cases. Platelet-derived MPs (PMPs) play a crucial role in the metastasis of BC, warranting specific focus. This study aimed to explore the involvement of procoagulant MPs in BC. **Methods:** This systematic review was carried out using the Preferred Reporting Items for Systematic reviews, and Meta-Analyses (PRISMA). Terms defined as MESH keywords were searched PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library searched in from 2011 to March 2024. Experimental and quasi-experimental studies were assessed by the CONSORT checklist. **Results:** Eventually, 15 studies were included. 426 participants were studied in the included articles. The potential clinical relevance of MPs as biomarkers in BC was indicated. Also, the role of MPs in immune modulation and multidrug resistance was approved. PMPs were found to enhance malignant features, including migration and invasion. Moreover, there were lower levels of MPs before neo-adjuvant chemotherapy, suggesting a potential impact of chemotherapy on MPs levels. The study highlights the remarkable capacity of multidrug-resistant BC-derived MPs to alter the phenotype and functionality of immune cells. **Conclusions:** The findings underscore the intricate interplay between MPs and cellular signaling pathways, shedding light on their potential as diagnostic biomarkers, and therapeutic targets in cancer. Specifically, the association between MPs levels and disease severity, as evidenced by their correlation with tissue-based biomarkers, tumor grading, and distant metastasis, highlights their clinical relevance in prognostication and risk stratification.

Keywords: Biomarker- Breast Cancer- Microparticle- Platelet

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Introduction

Breast cancer (BC), as a global challenge, is one of the most prevalent malignant diseases among women aged 20-50 years [1, 2]. In 2020, 2,261,419 new cases (11.7%) were diagnosed and 684,996 deaths (6.9%) were occurred [3]. The incidence of BC has been increasing steadily over the last decade, showing both absolute and relative rises in occurrence. It is projected that due to population growth and aging, there will be over 3 million new cases and more than 1 million deaths annually by 2040. The highest incidence rates for BC are found in Australia, New Zealand, North America, Northern Europe, and Western Europe, while the lowest rates are found in Africa, Central America, and Central Asia [4]. In 2020, 16967 BC were diagnosed in Iran and 4810 individuals from them died. This incidence rate was the highest among all cancer types [5]. BC is a malignant tumor originating in breast cells that can spread to distant parts of the body or invade nearby tissues [6]. Notably, the majority of cancer-causing agents (carcinogens) induce DNA sequence alterations or mutations. Therefore, similarly to all genetic diseases, cancer is caused by changes in DNA [7].

Microparticles (MPs) are tiny membranous vesicles, typically ranging from 0.05 to 1 μm in diameter, that are released from cell membranes in response to cellular activation, inflammation, and apoptosis [8-10]. These particles can originate from diverse cell types within the human body, including platelets, endothelial cells, red blood cells, synovial cells, smooth muscle cells, and cancer cells [9, 11]. MPs exhibit a heterogeneous nature, characterized by an intact phospholipid membrane and the expression of membrane antigens unique to their cell of origin. Although the conventional definition of MPs

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considers their size and the presence of externalized phosphatidylserine (PS) on the membrane, recent findings indicate that not all MPs expose PS on their surface, and the PS content may be linked to the origin of MPs, triggers, and/or their formation process [8].

Circulating MPs levels are increasingly elevated in many types of cancer, including hematologic malignancies, ovarian cancer, colorectal cancer, and BC [12]. Such vesicles carry genetic material derived from tumor cells as well as other tumor-derived biological molecules such as proteins and glycoconjugates that may affect the host systemically [13]. Studies have demonstrated that MPs are involved in the initiation, progression, and cancer metastasis. Additionally, their contributions to extracellular matrix repair, multidrug resistance, and modulation of inflammation, thrombosis, endothelial dysfunction, tissue regeneration, angiogenesis, and immunological responses have been documented [14, 15].

MPs hold promise as biomarkers for the diagnosis and prognosis of diseases [16]. In a study by Najjar et al., it was discovered that the elevation of circulating endothelial cells, and MPs during or after chemotherapy could act as predictive biomarkers for tumor progression in advanced lung cancer [17]. Janowska-Wieczorek et al., demonstrated that PMPs play a metastatic role in BC [18].

Furthermore, another study proposed that PMPs may have a significant impact on the pathogenesis and prognosis of BC [19]. The mechanisms by which MPs generate and detach from the cell plasma membrane are still largely unknown. Therefore, there is a need to further comprehend the underlying mechanisms that facilitate the transportation of specific proteins, RNA, and DNA by MPs. Hence, this systematic review was designed and carried out with the objective of examining the role of procoagulant MPs in BC.

Materials and Methods

This systematic review was conducted based on PRISMA guidelines. The code of ethics in this study was IR.JUMS.REC.1401.142, as issued by Jahrom University of Medical Sciences.

Search Strategy

A systematic literature search was conducted to identify relevant studies exploring the role of procoagulant MPs in BC. PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library were searched from 2011 to 2024 using a comprehensive search strategy. The search strategy included a combination of keywords and controlled vocabulary terms (MeSH terms) related to BC, procoagulant MPs, and synonyms. The search strategy was adapted for each database to ensure maximum coverage. Additionally, reference lists of included studies and relevant review articles were hand-searched to identify additional studies.

1. Procoagulant Microparticles (Text Word) OR Microvesicles (Text Word) OR Procoagulation (Mesh Term) OR Blood Coagulation (Mesh Term) OR Microparticles (Mesh Term) OR Blood Platelets (Mesh Term) OR Platelet Activation (Mesh Term) OR Thrombosis (Mesh Term) OR Blood Coagulation Disorders (Mesh Term) OR Blood Clotting (Mesh Term) OR Hemostasis (Mesh Term)

2. Breast Cancer (Text Word) OR Breast Neoplasms (Mesh Term) Breast Neoplasms/pathology (Mesh Term) OR Breast Neoplasms/therapy (Mesh Term) OR Breast Neoplasms/blood (Mesh Term) OR Breast Neoplasms/complications (Mesh Term) OR Breast Neoplasms/diagnosis (Mesh Term) OR Breast Neoplasms/surgery (Mesh Term)

3. 1 and 2

This search strategy combines terms related to procoagulant MPs and BC. It incorporates both text words and mesh terms to ensure comprehensive coverage of relevant literature. Adjustments to the specific terms and databases used may be necessary based on the search requirements.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

• Population: Human participants or animal samples diagnosed with BC.

• Intervention/Exposure: Studies investigating the presence or impact of procoagulant MPs in BC, either as a primary focus or as an outcome.

• Study Design: Original research studies, including observational studies (cohort, case-control, cross-sectional), clinical trials, and experimental studies.

• Outcome: Studies reporting outcomes related to the association between procoagulant MPs and BC progression, prognosis, or treatment response.

Studies not available in English, review articles, conference abstracts, letters, editorials, and studies with insufficient data for extraction were excluded.

Quality Assessment

Experimental and quasi-experimental studies were evaluated using the CONSORT checklist, which comprises 24 items [20]. Two authors independently assessed the quality of the included studies. In case of any disagreement, a third author was consulted. It is important to highlight that no study was excluded from this systematic review based on a low-quality assessment score.

Data Extraction

Two independent reviewers screened the titles and abstracts of all identified records to determine eligibility according to the predefined inclusion and exclusion criteria. Full-text articles of potentially eligible studies were obtained and evaluated for final inclusion. Data extraction was carried out using a standardized form, which included study characteristics (author, publication year, reference), participants, intervention/exposure details, sample type, laboratory techniques, outcome measures, and key findings related to the role of procoagulant MPs in BC. Any discrepancies between reviewers were resolved through discussion or by consulting a third reviewer if needed.

Results

A total of 15 studies were included in the analysis (Figure 1). All studies were experimental, except for one which was a case-control study. The studies were conducted in Australia (n=3), China (n=3), Iran (n=2), France (n=2), Brazil (n=2), Canada (n=1) and Germany (n=1)(Table 1). Also, the sample size was 426.

Cardiotoxicity Associated with MPs Levels

At baseline (T0), the cardiotoxicity group exhibited a significantly higher number of MPs compared to the control group (P=0.034). This observation suggests a potential association between elevated MPs levels and the development of cardiotoxicity in patients undergoing chemotherapy [21].

Doxorubicin Treatment and MPs Increase

In the cardiotoxicity group, there was an association between the increase in MPs levels and doxorubicin treatment. This finding implies a potential role of doxorubicin in inducing MPs release, contributing to the observed elevation in MPs levels in patients with chemotherapy-induced cardiotoxicity [22].

Impact of PMPs on Cancer Cells

PMPs were found to enhance malignant features, including migration and invasion, in cancer cells co-incubated with them. This observation suggests a potential mechanism by which PMPs promote cancer progression and metastasis [23].

Metabolic Plasticity Induced by PMPs

PMPs were associated with notable metabolic plasticity and the release of mito MPs-packaged mitochondria. This finding suggests a potential link between MPs and cancer aggressive processes, implicating them in tumor metabolism and progression [24].

Association of MPs with BC Characteristics

Patients with BC exhibited a significantly higher rate of PMPs compared to normal subjects (P<0.001). Additionally, significant and positive correlations were observed between MPs levels and tissue-based biomarkers, tumor grading, and distant metastasis (P<0.05), indicating the potential clinical relevance of MPs as biomarkers in BC [25, 26].

MPs and Chemotherapy-Induced Change

BC patients treated with paclitaxel chemotherapy showed increased levels of *CD44*-expressing tumor-derived MPs (P<0.001). Additionally, lower levels of MPs were observed before neo-adjuvant chemotherapy, indicating a potential influence of chemotherapy on MPs levels. [27].

MPs in Multidrug Resistance and Immune Modulation

MPs shed from multidrug-resistant cells were found to selectively polarize macrophage cells and alter the phenotype and functionality of immune cells. Additionally, drug-resistant BC-derived MPs were associated with the presence of specific proteins (Ezrin, radixin, moesin, and talin-1), suggesting a potential role in immune modulation and multidrug resistance [28, 29].

MPs and Thrombogenicity

Cancer cell-derived extracellular vesicles, including MPs, induced a procoagulant shift in endothelial cells, displaying tissue factor activity and enhancing thrombin generation. Furthermore, higher tissue factor activity was

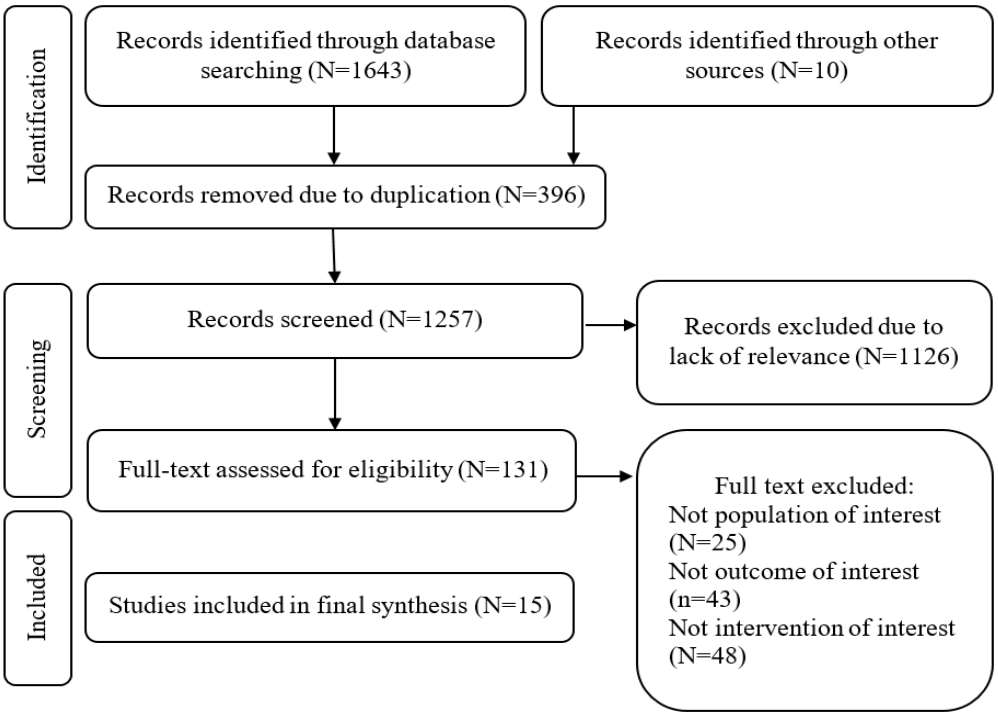

Figure 1. PRISMA Flowchart of Selected Studies

Table 1. Overview of Included Studies

Author, Year, Reference	Location	Study Type	Participants (Number)	Sample Type	Laboratory Techniques	Outcome Measure	Key Finding
Pestana et al. (2024) [21]	Brazil	Prospective observational study	Women with clinical and histopathology diagnosis of BC undergoing doxorubicin-based chemotherapy (n=80)	Cardiomyocytes and platelets	Centrifugation	Association of MPs and cardiotoxicity	- Higher number of MPs in the cardiotoxicity group at T0 [P=0.034) - Association of the increase in the MPs and doxorubicin treatment in the cardiotoxicity group
Veilleux et al. (2024) [24]	Canada	Experimental	Not mentioned	Platelet	Not mentioned	The impact of mito MPs on BC metabolic reprograming and phenotypic processes leading to malignancy	- Various cells involved in recipient cell permeability to PMPs internalization - Enhanced malignant features in terms of migration and invasion in cancer cells co-incubated with PMPs - Association between mito MPs -packaged mitochondria and cancer aggressive processes and notable metabolic plasticity induced by PMPs
Ranjbaran et al. (2022) [25]	Iran	Experimental	Not applicable	MDA-MB-231 cell	Centrifugation and Flow cytometry	Procoagulant activity of MPs expressing PS derived from BC cell line MDA-MB-231	- The increase in the total number of MPs (P<0.001) - Association between adriamycin and increased level of procoagulant activity of tumor-derived MPs
Yang et al. (2021) [53]	China	Retrospective	Not applicable	Platelets and 4T1 cells	Thromboelastography and optical in vivo imaging	Hypercoagulable status characterized by platelet activation in the context of promoting hematogenous metastasis	- Contribution of coculture of platelets and 4T1 cells to the release of extracellular vesicles and the development of the hypercoagulable status - Direct association between breast tumor, volume, and weight with tumor-bearing period
Zhang et al. (2021) [22]	China	Experimental	Healthy individuals (n=20) and patients undergoing neoadjuvant chemotherapy with doxorubicin and cyclophosphamide	Blood	Fluorescence-activated cell sorting, flow cytometry and electron microscopy	Chemotherapy-induced BC cell-derived MPs and coagulation time, fibrin formation, and expression of intrinsic/extrinsic factor Xase (FXa) and thrombin	- Association between pretreatment with lactadherin and uptake of chemotherapy-induced BC cell-derived MPs for subsequent activation of platelets - Effective role of incubation with doxorubicin for releasing large numbers of chemotherapy-induced BC cell-derived MPs and PS
Haghbin et al. (2021) [23]	Iran	Case-control	Patients with BC (n=30) and normal subjects (n=20)	Platelet	Centrifugation and Flow cytometry	The levels of platelet-derived MPs	- Significantly higher rate of PMPs in the BC patients than normal subjects (p<0.001) - Significant and positive correlations between PMPs levels and tissue-based biomarkers, tumor grading, and distant metastasis (P<0.05) - No significant correlation between tumor histological type and PMPs (p=0.065)
Shechter et al. (2020) [33]	Germany	Experimental	Not applicable	MDA-MB-231, 4T1 and HEK293T	Modified Boyden Chamber Assay, Pillar Fabrication, Western blot, The ex vivo pulmonary metastasis assay (PuMA) and cell viability Alamar BlueTM Assay	The involvement of tumor-derived MPs as mediators of the metastatic switch in the tumor microenvironment by hindering cell adhesion properties	- Capability of tumor-derived MPs to substantially reduce cell adhesion and disrupt actin filament structure (P<0.05) - Capability of CD44 to meditate pro-metastatic effects (P<0.05) - Increased level of CD44-expressing tumor-derived MPs in BC patients treated with paclitaxel chemotherapy (P<0.001)
Djedidi-Amrane et al. (2020) [32]	France	Experimental	Not Applicable	Plasma and umbilical vein endothelial cells	Cell culture, Procoagulant phospholipid-dependent clotting time, Calibrated Automated Thrombogram assay and Trizol Reagent	Comparing tissue factor activity in BC cells and pancreas adenocarcinoma cells	- Ability of cancer cell derived extracellular vesicles to lead to a procoagulant shift of endothelial cells, displaying tissue factor activity and enhancing thrombin generation - Higher tissue factor activity in pancreas adenocarcinoma cells compared with BC cells (P<0.05)

Table 1. Continued

Author, Year, Reference	Location	Study Type	Participants (Number)	Sample Type	Laboratory Techniques	Outcome Measure	Key Finding
Zhang et al. (2019) [30]	China	Experimental	BC patient treated with neo-adjuvant chemotherapy (n=25) and healthy controls (n=20)	Blood	Fluorescence-activated cell sorting	Properties of MPs derived from BC cells following exposure to high- or low- dose chemotherapeutic agents	- Lower levels of MPs before neo-adjuvant chemotherapy - Shorter clotting time of whole blood after neo-adjuvant chemotherapy - Capability of MPs derived from BC cells to thrombogenicity and inducing platelet activation or even apoptosis, leading to higher procoagulant activity
Gomes et al. (2017) [34]	Brazil	Experimental	Not mentioned	MDA-MB-231, MCF-7 and platelets	Western blotting, plasma clotting and platelet aggregation	Platelet activation, aggregation and plasma coagulation, in experiments that access both tissue factor-dependent and -independent activities.	- Higher tissue factor protein levels and tissue factor-dependent procoagulant activity in MDA-MB-231 compared with MCF-7 - Higher induction of tissue factor-dependent platelet aggregation in the MDA-MB-231 compared with MCF-7
Jaiswal et al. (2017) [28]	Australia	Comparative Experimental	Not applicable	THP1 and MCF-7	Western blotting, Flow cytometry and Confocal microscopy		- Capability of MPs shed from multidrug resistant cells to selectively polarize macrophage cells and facilitate their engulfment by foreign cells - remarkable capacity of multidrug resistant BC derived MPs to alter the phenotype and functionality of immune cells
Pokharel et al. (2014) [29]	Australia	Experimental	Not applicable	MCF-7	Western blotting, liquid chromatography-tandem mass spectrometry and Sodium dodecyl-sulfate polyacrylamide gel electrophoresis	Proteome of BC-derived and differences in protein profiles between those shed from drug-resistant versus drug-sensitive BC cells	- Presence of Ezrin, radixin, moesin and talin-1 only in MPs derived from drug-resistant cells - Occurring the MPs-mediated transfer of P-gp to recipient cells alongside CD44; the Ezrin, Radixin and Moesin protein family
Chaari et al. (2014) [27]	France	Experimental	BC patients using chemotherapy for at least 21 days (n=62) and healthy controls (n=30)	Platelet	Flow Cytometry	The potential relation between cancer-related characteristics and the biomarkers of plasma and cellular hypercoagulability	- Significantly higher levels of PMPs in patients with metastatic disease - Significantly higher thrombin generation in patients receiving chemotherapy with less than 6 months since diagnosis
Jaiswal et al. (2013) [26]	Australia	Experimental	Not applicable	human malignant cell lines and mammary basal epithelial cells	Confocal microscopy and flow cytometry	Tissue Selectivity in the Transfer of Resistance Proteins to Cells	- CD44 (isoform 10) as the selective transporter of P-glycoprotein to malignant breast cells observed ($P<0.05$) - Stable transfer of P- glycoprotein by MPs after using the MCF-7 ($P<0.05$)
Trappenburg et al. (2011) [31]	Netherland	Experimental	BC patients using endocrine therapy (n=40) and healthy controls (n=20)	Plasma	Flow cytometry and Calibrated Automated Thrombogram	The level of MPs in patients receiving and not receiving endocrine therapy	- Association between Thrombin generation in plasma and the level of MPs - Higher levels of MPs in patients receiving endocrine therapy ($P=0.03$)

Table 2. An overview of quality assessment of studies using CONSORT checklist

Author and year of publication	CONSORT score
Pestana et al. (2024)	21/25
Veilleux et al. (2024)	20/25
Ranjbaran et al. (2022)	22/25
Yang et al. (2021)	22/25
Zhang et al. (2021)	20/25
Haghbin et al. (2021)	21/25
Shechter et al. (2020)	21/25
Djedidi-Amrane et al. (2020)	22/25
Zhang et al. (2019)	22/25
Gomes et al. (2017)	22/25
Jaiswal et al. (2017)	23/25
Pokharel et al. (2014)	21/25
Chaari et al. (2014)	20/25
Jaiswal et al. (2013)	20/25
Trappenburg et al. (2011)	22/25

observed in pancreas adenocarcinoma cells compared with BC cells, indicating potential differences in thrombogenicity among cancer types [30].

Association with Treatment and Therapeutic Response

Patients receiving endocrine therapy exhibited higher levels of MPs compared to those not receiving such therapy (P=0.03), suggesting a potential association between treatment modality and MPs levels [31].

MPs Correlation with Thrombin Generation

Thrombin generation in plasma was found to be associated with the level of MPs, highlighting the potential link between MPs and thrombotic events [32].

Role of CD44 in Mediating Pro-Metastatic Effects

CD44, a cell surface glycoprotein involved in cell-cell interactions and signaling, was identified as a mediator of pro-metastatic effects (P<0.05). The presence of *CD44*-expressing tumor-derived MPs suggests their involvement in promoting cancer metastasis through interactions with the extracellular matrix and facilitating tumor cell dissemination. BC patients treated with paclitaxel chemotherapy exhibited an increased level of *CD44*-expressing tumor-derived MPs (P<0.001). This finding suggests a potential impact of chemotherapy on the release of *CD44*-positive MPs, potentially contributing to chemotherapy resistance and metastatic progression [33].

Differential Tissue Factor Levels and Procoagulant Activity

MDA-MB-231 BC cells demonstrated higher tissue factor protein levels and tissue factor-dependent procoagulant activity compared to MCF-7 cells. This observation indicates potential differences in thrombogenicity between BC cell lines, with MDA-MB-231 cells exhibiting a higher propensity for inducing coagulation and platelet aggregation. MDA-MB-231 BC cells also showed a higher induction of tissue factor-dependent platelet aggregation compared to MCF-7 cells. This finding further supports the notion of increased thrombogenicity associated with certain BC cell types, highlighting the potential contribution of tissue factor to cancer-associated coagulopathy and thrombotic events. [34].

Quality Assessment

An overview of quality assessment of studies using CONSORT checklist is presented in Table 2.

Discussion

The systematic review conducted provides valuable insights into the complex interplay between platelets, BC cells, extracellular vesicles (EVs), and the hypercoagulable state. The findings highlight various mechanisms that contribute to tumor progression, treatment response, and thromboembolic complications, shedding light on potential avenues for therapeutic intervention. The systematic review conducted offers valuable insights into the role of PMPs and thrombin generation in cancer progression and treatment response. The findings underscore the complex interplay between hemostatic factors and metastatic disease, shedding light on potential biomarkers and therapeutic targets for cancer management. In addition, this study presents intriguing findings regarding the capability of MPs shed from multidrug-resistant cells to modulate immune cell behavior and facilitate their engulfment by foreign cells. These results shed light on the complex interplay between cancer cells, immune cells, and drug resistance mechanisms, with potential implications for cancer progression and treatment.

One of the key findings of this review is the significantly higher levels of PMPs in patients with metastatic disease. This observation is consistent with previous studies demonstrating the role of platelet activation and MPs release in cancer metastasis [35]. PMPs not only contribute to thrombosis and tumor cell dissemination but also facilitate immune evasion and angiogenesis within the tumor microenvironment. The elevated levels of MPs in patients with metastatic disease highlight their potential utility as biomarkers for disease progression and prognosis, offering opportunities for early detection and targeted interventions [36]. Moreover, the review identifies significantly higher thrombin generation in patients receiving chemotherapy with less than 6 months since diagnosis. Thrombin, a key mediator of coagulation, plays a crucial role in tumor progression, angiogenesis, and metastasis [37]. Chemotherapy-induced thrombin generation may reflect increased tumor burden, inflammation, and endothelial dysfunction, contributing to the hypercoagulable state observed in cancer patients. The association between thrombin generation and time since diagnosis underscores the dynamic nature of cancer progression and its impact on hemostatic balance, highlighting the importance of early intervention to mitigate thrombotic complications in cancer patients [38]. However, while the findings regarding PMPs and thrombin generation are in line with previous research,

there are also inconsistent findings in the existing literature. Some studies have reported conflicting results regarding the association between PMPs and cancer metastasis [39]. While elevated levels of MPs have been observed in patients with advanced disease, other studies have failed to demonstrate a significant correlation with metastatic spread. These discrepancies may be attributed to variations in patient populations, tumor types, and analytical techniques, underscoring the need for further research to elucidate the underlying mechanisms.

Similarly, conflicting findings exist regarding the association between thrombin generation and chemotherapy in cancer patients. While some studies have reported increased thrombin generation following chemotherapy initiation [40], others have failed to observe significant changes [41]. Variations in chemotherapy regimens, treatment response, and patient characteristics may contribute to these inconsistent findings. Additionally, the timing of thrombin generation assessment relative to chemotherapy initiation may influence the observed outcomes, highlighting the importance of longitudinal studies to capture dynamic changes in hemostatic parameters over time [42].

One of the key findings of this review is the significant contribution of coculture of platelets and 4T1 BC cell line to the release of EVs and the development of a hypercoagulable status. This observation is consistent with previous studies demonstrating the crucial role of platelets in promoting cancer progression through the release of EVs and activation of coagulation pathways [43]. The interaction between platelets and cancer cells within the tumor microenvironment facilitates tumor growth, angiogenesis, and metastasis, underscoring the importance of targeting platelet-mediated mechanisms in cancer therapy [44].

The association between pretreatment with lactadherin and uptake of chemotherapy-induced BC cell-derived MPs for subsequent activation of platelets, introduces a novel therapeutic approach with potential implications for improving treatment outcomes. Lactadherin, an annexin family protein, has been shown to enhance the clearance of apoptotic cells and promote anti-inflammatory responses [45]. By facilitating the uptake of chemotherapy-induced MPs and subsequent activation of platelets, lactadherin may enhance the efficacy of chemotherapy, while minimizing thromboembolic complications in BC patients [46]. Regarding lactadherin pretreatment and MPs uptake, while the systematic review suggests a potential association between lactadherin and enhanced uptake of chemotherapy-induced BC cell-derived MPs, there are inconsistent findings in the existing literature. Some studies have reported a significant increase in MPs uptake and subsequent platelet activation following lactadherin pretreatment [47], whereas others have failed to demonstrate a significant effect [48].

The study highlights the remarkable capacity of multidrug-resistant BC-derived MPs to alter the phenotype and functionality of immune cells. This finding is supported by previous research demonstrating the immunomodulatory effects of cancer-derived MPs, including immune cell activation, polarization, and suppression [49]. The ability of these MPs to induce phenotypic and functional changes in immune cells may contribute to tumor immune evasion, progression, and metastasis, posing challenges for cancer therapy [50]. Moreover, the study underscores the capability of multidrug-resistant cell-derived MPs to selectively polarize macrophage cells and facilitate their engulfment by foreign cells. Macrophages play a critical role in tumor progression and metastasis, with distinct phenotypes exerting either pro-tumorigenic or anti-tumorigenic effects [51]. However, while the findings regarding the immunomodulatory effects of multidrug-resistant cell-derived MPs are compelling, there are also inconsistent findings in the existing literature. Some studies have reported conflicting results regarding the impact of cancer-derived MPs on immune cell polarization and function [52].

Future research should focus on clarifying the underlying mechanisms of MPs-mediated pathophysiology and exploring their potential as therapeutic targets. Specifically, investigating the molecular pathways involved in MPs-induced immune modulation, thrombogenicity, and chemotherapy resistance could reveal novel therapeutic strategies to reduce disease progression and treatment complications. Additionally, longitudinal studies are needed to evaluate the prognostic value of MPs levels in predicting treatment response, disease recurrence, and overall survival in cancer patients. In general, continued exploration of the role of MPs in disease pathogenesis and their therapeutic potential is crucial for advancing our understanding and improving clinical outcomes in cancer.

Limitations

Some limitations need to be addressed. Initially, only four databases were searched, and the search was restricted to English language studies. Additionally, the full text of certain eligible studies was unavailable. Furthermore, this study did not conduct a meta-analysis, making it challenging to assess the quality of the results. Despite these limitations, this systematic review provided valuable insights into the significance of circulating procoagulant MPs in BC.

In conclusions, this systematic review provides a comprehensive insight into the diverse roles of MPs in various pathophysiological processes, ranging from cancer progression to chemotherapy-induced cardiotoxicity and hypercoagulability. The study highlights the complex interactions between MPs and cellular signaling pathways, revealing their potential as both diagnostic biomarkers and therapeutic targets in cancer. Notably, the correlation between MPs levels and disease severity, is demonstrated through their association with tissue-based biomarkers, tumor grading, and distant metastasis, emphasizes their clinical significance in prognosis and risk assessment. Additionally, the capacity of MPs to influence immune cell phenotype and function, along with their participation in thrombotic events, underscores the importance of targeting MPs-mediated mechanisms in disease management.

Author Contribution Statement

MH, and AHT contributed to the conception and design of the study. AHT, and ASJ acquired and analyzed the data. AHT, and ZGN contributed to the writing of the manuscript. All the authors read and approved the final manuscript.

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Scientific Approval

This systematic review is a component of Zahra Ghasemi Nejad MD thesis.

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Statement of Ethics

The procedure of study was approved by the ethics committee of Jahrom University of Medical Sciences (IR.JUMS.REC.1401.142). This study does not require informed consent.

Conflicts of Interest

The authors declare that they have no relevant financial or non-financial conflicts of interests to disclose.

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