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Extracellular vesicles and microRNAs in surgical disease: Emerging biomarkers of tissue injury, inflammation, and postoperative recovery

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Abstract

The surgical wound creates a systemically co-ordinated response of cell stress, inflammation, endothelial activation, tissue injury and repair. The ability of Extracellular Vesicles (EVs), such as microvesicles and exosomes, to transfer biological information between cells via proteins, lipids and nucleic acids is being increasingly acknowledged. One class of compounds of particular interest is microRNAs (miRNAs), which can be selectively loaded into EVs, and represent the condition of EVs releasing cells and can mediate gene expression in recipient tissues. The findings from this narrative review highlight the new emerging concepts of EVs and EV-associated miRNAs as biomarkers and signalling agents in surgical disease. An overview of evidence related to AKI in cardiac surgery, postoperative sepsis and septic shock, postoperative delirium and neurocognitive dysfunction, congenital cardiac surgery, and tissue repair is provided. The review highlights differences between biomarker correlation and mechanistic causation and considers how EVs concentration, surface phenotype, cellular origin and molecular cargo can be used in addition to traditional clinical data analysis. This is despite methodological limitations such as the lack of a uniform method for EV isolation, pre-analytical variability, incomplete particle characterisation, miRNA normalisation, and the lack of external validation. However, new studies in the last few years have revealed that signatures derived from EVs may aid in cell non-invasive discrimination of postoperative complications and may offer an early 'liquid-biopsy window' into tissue injury prior to peak evolution of conventional markers. The next steps should be to test whether cargo in EVs could be manipulated in a therapeutic way to enhance postoperative recovery, to introduce multimodal phenotyping of EVs in a standardised way and change towards longitudinal sampling and validation of the EVs in terms of postoperative outcome.

Keywords: Surgical wound, MicroRNAs, Tissue injury, Inflammation, Biomarkers

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1. Introduction: From surgical injury to circulating molecular signals

Biological disturbance caused by major surgery is significantly greater than many will realize from the actual

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physical wound generated by the surgery. Signals are released in the circulation as a result of tissue discontinuity, haemodynamic instability, blood loss, anaesthetic, ischaemia-reperfusion, inflammatory activation, transfusion and organ stress which could impact distant tissues. Conventional peri-op markers like creatine, lactate and C-reactive protein or Troponin are clinically valuable markers but many are markers of downstream reactions and are not markers of the initial molecular response to a tissue injury. EVs and their cargo of molecules have thus been studied as a possible dynamic index of cellular stress and inter-organ communication (Théry *et al.*, 2018; Welsh *et al.*, 2020; Kalluri and LeBleu, 2020; van Niel *et al.*, 2018).

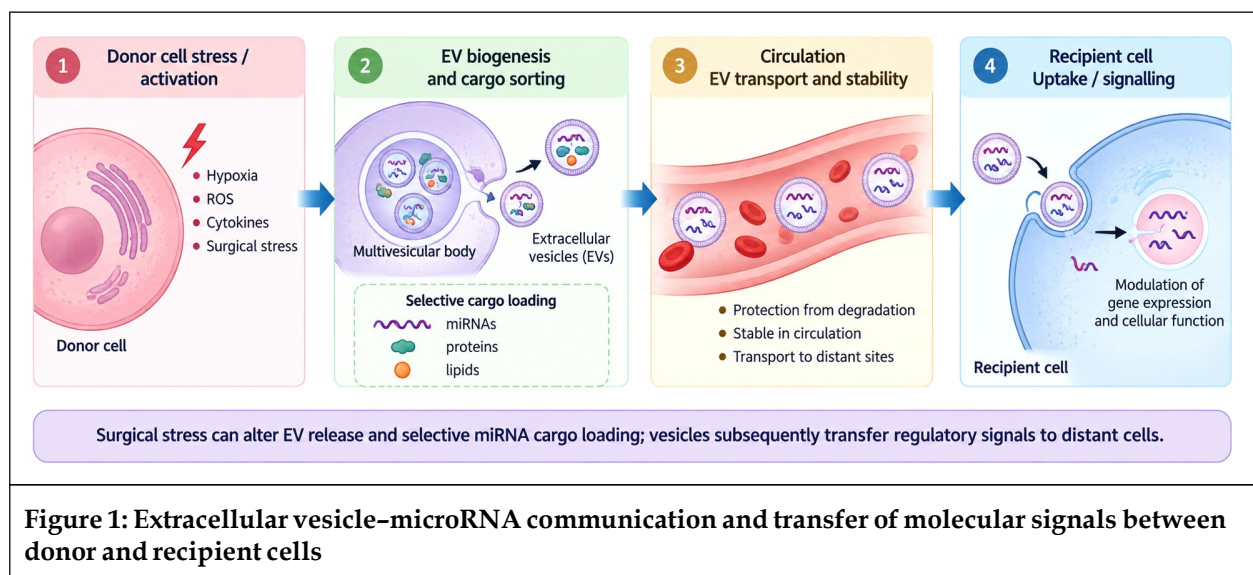
All types of cells shed EVs. They can transport proteins, lipids, messenger RNAs, miRNAs, long non-coding RNAs and fragments of DNA. The vesicles' membrane can shield nucleic acids from extracellular degradation, so that EV-associated miRNAs are detectable in biofluids, and potentially contain information about the cell of origin and its physiological state (Valadi *et al.*, 2007; O'Brien *et al.*, 2020; Arroyo *et al.*, 2011; Turchinovich *et al.*, 2011). This suggests an inherent conceptual benefit of using an EV compared to measurement of freely circulating nucleic acids because EVs can be thought of as bioactive packages that are able to transport information to another cell.

Surgical environment is well-suited to explore such biology as the time of the injury is fairly well controlled. Preoperative samples can be used to derive a first set of molecular phenotypes, and serial postoperative samples can be used to sample the molecular trajectory of an uncomplicated recovery or the development of complication(s). Signatures of EVs and miRNAs have been recently reported in the context of acute kidney injury following cardiac surgery, postoperative septic shock and postoperative delirium, providing evidence of the potential of EV profiling, as a form of molecular-liquid biopsy, for the perioperative setting (Miller *et al.*, 2022; Crit Care, 2025, Cho *et al.*, 2024; Xu *et al.*, 2025).

2. Extracellular vesicles and microRNAs: Biology, classification, and cargo

Extracellular vesicles are often spoken of as exosomes, microvesicles and/or apoptotic bodies, but international guidelines currently focus on the fact that one should not discuss these types of extracellular vesicles solely according to their size, as there are fuzzy borders between them and isolation techniques are not always precise. It is most often thought of in the context of the endosomal multivesicular-body pathways, while microvesicles are formed by outward budding of the plasma membrane. During programmed cell death, "apoptotic bodies" are formed and can contain relatively large cell components. The more appropriate term for clinical studies is 'extracellular vesicles' unless it has been shown that they are actually biogenic.

EVs are not only due to particle abundance, the biological importance is also dependent on molecular cargo and their cellular origin. Different molecular signatures can be found on endothelial-, platelet-, leucocyte-, epithelial-, stromal- and tumour-derived EVs. These changes in surface proteins could be associated with change in biodistribution and uptake by recipient cells, and change in the inflammatory or metabolic response may be mediated by changes in lipid or protein composition (Mathieu *et al.*, 2019; Yáñez-Mó *et al.*, 2015;



Raposo and Stoorvogel, 2013). The number of circulating EVs and the type of EVs can therefore be altered by surgical injury.

MicroRNA are short, non-coding RNA molecules which acts as small pieces to regulate gene expression primarily by sequence specific binding to target messenger RNA molecules. Their inclusion in EVs may not be random as there are cellular stress factors and RNA-binding proteins that can affect sorting depending on cell type and context (Villarroya-Beltri *et al.*, 2013; Koppers-Lalic *et al.*, 2014). So an up-regulated of a certain EV-miRNA after surgery may be a signal of either transcription change from the source cell or selectivity in loading, or increased release of EVs and/or clearance or a combination of one or more of these.

Table 1: EV classes, cargo and potential relevance to surgical disease

EV category	Typical origin/biology	Relevant cargo	Potential surgical relevance
Exosome-enriched small EVs	Endosomal multivesicular-body pathway	miRNAs, proteins, lipids	Intercellular signalling; candidate liquid biomarkers
Microvesicles/larger EVs	Plasma-membrane budding	Membrane proteins, miRNAs, mRNA, lipids	Endothelial/platelet activation and inflammatory signalling
Apoptotic bodies	Cell disassembly during apoptosis	DNA, organelles, proteins, RNAs	Tissue injury and clearance
Cell-specific EV populations	Endothelial, platelet, immune, epithelial, stromal sources	Source-specific surface markers and cargo	Potential attribution of organ-specific injury

3. Surgery as a trigger of EV release and miRNA reprogramming

The perioperative period harbors multiple factors that can modify EV biology, including hypoxia, oxidative stress, inflammatory cytokines, mechanical stress, cell death and changes in cellular metabolism (Loyer *et al.*, 2014; Burger *et al.*, 2013; Jansen *et al.*, 2017). Endothelial cells may secrete EVs upon activation, platelets may evolve a lot of circulating EVs and sick parenchymal or epithelial cells may modify exocytosis of vesicles. Therefore, the postoperative EV should be seen as a conglomerate signal and not as a direct report from a single damaged organ.

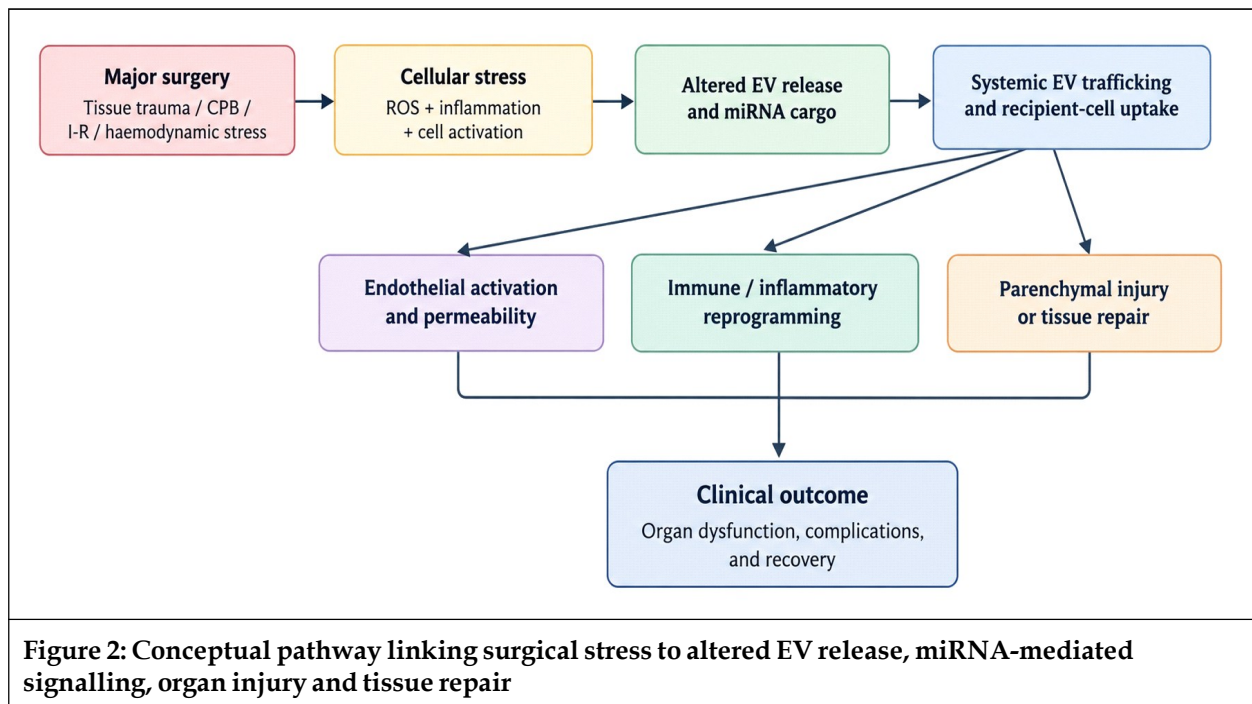
That's a good and bad thing in one. The EV signature could be a composite one combining multiple characteristics of the systemic response and hence serve as a predictor of clinical deterioration. But, in the absence of powerful surface markers or molecular attributions, it can be challenging to decide where an observed miRNA has come from, perhaps kidney, endothelium, immune cells or platelets. This translates to significance when trying to decipher the mechanistic interpretation of EV-miRNA changes statistically instead of just mechanistically (Théry *et al.*, 2009).

Serial sampling might be a way to help solve this issue. A biomarker that occurs earlier before the organ dysfunction is happening more desirable than a biomarker that only increases once this organ dysfunction has been present. The 2022 cardiac-surgery AKI study is illustrative, as changes in urinary EV and miRNA were evaluated pre- and 24 hours post-surgery, and preoperative podocalyxin-positive EVs, urinary particle concentrations and miR-125a-5p were used to create an AKI prediction model.

4. EV-miRNA signalling in inflammation, tissue injury, and organ dysfunction

Receptor-mediated uptake, endocytosis and surface-receptor interaction, and membrane fusion are ways EVs can affect the recipient cells. They are then able to change transcription programs of endothelial cells, immune cells, epithelial cells and stromal populations (Mathieu *et al.*, 2019). In surgical disease, this offers a reasonable explanation as to how a local tissue insult can manifest as a generalized or organ-specific inflammatory response.

In the field of endothelial biology, EVs can alter the permeability of the endothelial layer, the adhesion of leukocytes and coagulatory and angiogenic signals. Platelet-derived vesicles might be involved in inflammatory and thrombotic signaling and immune-cell-derived EVs might supply inflammatory mediators or regulatory RNAs (Owens and Mackman, 2011; Nomura, 2017). Such effects are potentially applicable to the postoperative



capillary leak, microcirculatory dysfunction and organ injury, as endothelial activation is a shared intermediate phenotype in a number of postoperative complications. Not only injury, but EV-miRNAs could also be involved in the repairing of damages. EVs derived from stromal cells and/or mesenchymal cells have also been explored and shown to harbor regulatory RNAs that can act to enhance angiogenesis, suppress inflammatory signalling and aid cell survival (Kalluri and LeBleu, 2020; Mendt *et al.*, 2018; Phinney and Pittenger, 2017; Vader *et al.*, 2016). It needs to be emphasized that, on the one hand, the postoperative EV pool can contain both pathogenic and reparative signals and, on the other hand, changes in EV-miRNA cannot be represented by the direction of the change alone.

5. Clinical evidence across surgical diseases

In the case of EV-miRNA biomarkers, one best example is the discovery of acute kidney injury after cardiac surgery. In 94 cardiac-surgery patients, we have urinary EVs and miRNAs following cardiac surgery and generated an increase in urinary particle concentration following surgery on patients who go on to develop AKI, as found by Miller *et al.* the number of EVs that expressed Podocalyxin was found to be reduced from preoperatively in the patients with AKI similarly, miR-125a-5p was down regulated from urine before surgery, and a combination of EV measures, miR-125a-5p and ICU lactate gave an AUC of ~0.82. These findings are significant and indicate that urinary EVs could reflect renal stress earlier and/or differently than serum creatinine.

Diagnostic discrimination is even more directly evaluated by postoperative sepsis. A recent multicentre prospective study consisted of 109 patients in a discovery cohort and 52 patients in a validation cohort; the authors were able to identify 30 EV-derived miRNAs that were altered in septic compared to non-septic shock. In a discovery cohort, the AUC of the 3-miRNA signature (miR-100-5p, miR-148a-3p and miR-451a) was 0.894, which was validated by qPCR to 0.960. The power of this study is not only the number of miRNAs identified, but that the study should be a prospective multicentre study which is externally validated (and also broader validation needed).

Another growing use is postoperative delirium and neurocognitive dysfunction. A recent 2024 machine learning study was conducted by Matuska *et al.*, who profiled plasma EV-miRNAs in a cohort of 31 patients who developed postoperative delirium after undergoing spine surgery and in 31 matched, contemporary controls. A list of 142 miRNAs were identified as being DE, selected candidates were then confirmed in an independent sample set of 96 participants. In a different recently published miRNA serum exosome study, 57 miRNAs were found to be differently expressed in postoperative delirium, and a number of pathways related to neurotrophin signalling, neuronal plasticity and cell viability were enriched.

The neuro-literature also serves as a prime example of the first pillar of science: biomarker association, moving to both mechanistic interpretation. Recently studies in hip and knee replacement patients have shown protein and miRNA levels in EVs differ between patients showing postoperative cognitive decline versus postoperative cognitive improvement, suggesting that EV signalling is involved in the neurocognitive trajectory following surgery (Br J Anaesth, 2025). But these studies are still relatively small-sized, and should be viewed as hypothesis-generating rather than proof of cause.

Recovery may be accomplished by EV biology. Changes in EV-associated miRNA patterns involved in angiogenesis, cell migration and regenerative processes have been reported in studies of EVs in the postoperative setting in congenital cardiac surgery ([Postoperative extracellular vesicles and miRNA-associated regenerative signalling after congenital cardiac surgery, 2024](#)). This implies that this biological system, which signals injury in tissues, can also signal reparative responses. The clinically relevant question might thus not be 'is EV-miRNA up-regulated?', but rather 'what does the dynamic EV cargo say about the ratio between injury, inflammation and repair?'

Table 2: Representative clinical studies evaluating extracellular vesicle-microRNA signatures as biomarkers of postoperative injury, complications, and recovery across different surgical settings

Surgical setting	EV/miRNA finding	Outcome	Study signal
Cardiac surgery	Urinary EV concentration, podocalyxin-positive EVs, miR-125a-5p and miR-10a-5p	AKI	EV/miRNA variables improved prediction when combined with lactate
Postsurgical shock	30 EV-miRNAs; 3-miRNA signature validated	Septic vs non-septic shock	AUC 0.894 discovery; 0.960 validation
Spine surgery in older adults	142 differentially expressed plasma EV-miRNAs	Postoperative delirium	Top candidates validated by qRT-PCR
General elderly surgical population	57 altered serum exosomal miRNAs	Postoperative delirium	Pathways included neurotrophin and neuronal signalling
Hip/knee replacement	Differential EV proteins and miRNAs	Postoperative cognitive decline/recovery	Potential signalling role; early mechanistic evidence
Congenital cardiac surgery	Postoperative EV-miRNA changes	Recovery/regenerative response	Signals related to angiogenesis and cell migration

6. EVs and miRNAs as biomarkers of postoperative recovery

A clinically useful biomarker is one that will affect management, not a statistically significant difference. EV-miRNAs have several theoretical advantages: (1) They are measurable in human blood or urine; (2) their lipid bilayer provides protection from RNA degradation; and (3) their contents may be indicative of the original cell and the state of the cell. Thus their use would be widespread: in the algorithm of risk stratification prior to surgery; in the early detection of postoperative complications; and for long-term monitoring of postoperative recovery.

Preoperative risk prediction is especially appealing for complications whose clinical manifestation takes place subsequent to an irreversible phase of injury. Cardiac-surgery AKI study revealed that information was contained in pre-operative EV and miRNA measures prior to clinically evident postoperative AKI. Also, the postoperative delirium study showed that EV-miRNA differences were present close to the time of clinical identification and prior to postoperative delirium.

There should be a shift towards avoiding single miRNA searching as biomarkers though. The surgery-induced tissue trauma is considered a wide-spread perturbations of the entire biological system (miRNA can change by hundreds). A more clinically realistic approach, involves multimodal modelling, which includes EV abundance, EV surface phenotype, selected miRNA panel, conventional laboratory value and clinical variables. These models should be trained and validated in a prospective fashion and be calibrated, evaluated for clinical net benefit and examined for transportability between surgical populations.

Using longitudinal measurement may in the end be more useful than a single post-operative measurement. Prolonged or secondary EV-miRNA fluctuation might constitute a tool to recognize patients with a tendency

to organ failure; transient might be a sign of normal injury/repair. This is a trajectory based approach rather than a single threshold to better reflect the biology of postoperative recovery.

Table 3: Clinical stages, potential applications, advantages, and major limitations of extracellular vesicle-microRNA biomarkers in perioperative care			
Clinical stage	Potential application	Advantage	Major limitation
Preoperative	Risk prediction for AKI, delirium and other complications	May identify vulnerability before overt injury	Baseline heterogeneity and confounding
Early postoperative	Detection of tissue injury or sepsis	Potentially earlier than conventional markers	Need validated timing and cut-offs
Serial monitoring	Trajectory of injury vs recovery	Captures dynamic biological response	Repeated sampling and normalisation
Mechanistic phenotyping	Identify source/cargo/pathway	May link biomarker to mechanism	Cell-of-origin attribution remains difficult

7. From biomarker to mechanistic and therapeutic target

A fundamental paradigm change in the field has been the perception of EVs as passive reporters of cell identity to their active role as mediators of intercellular communication. Once an EV population is detected before an adverse outcome and the contents of the EV have been seen to modify the behaviour of a recipient cell within an experimental system, the EV is a legitimate target for determination of a possible mechanistic process, instead of just being a diagnostic marker.

At least in theory there are various levels at which therapeutic approaches can work, both by preventing the release of pathogenic EVs and by blocking uptake of EVs by susceptible recipient cells; by modifying EV cargo; by selectively removing harmful EVs; and by delivery of engineered/reparative EVs. Due to its immunomodulatory and regenerative effects, EVs derived from MSCs have been the subject of special interest; however, their application in the perioperative setting is still under investigation.

One of the biggest issues is indiscriminate suppression of EV release could be counterproductive. Both positive and negative signals are expressed on EVs; and the same pathway is beneficial in one tissue and detrimental in another. It is therefore necessary to think in terms of cell-of-origin and cargo targeting for therapeutic development, as that is what characterizes EVs in circulation as a pathogenic entity.

Another growing potential is that of 'engineered EVs'. Such expression of selected RNAs or proteins could, in the future, help to promote healing of tissues, control excessive inflammation or to adjust endothelial dysfunction. Prior to clinical use, however, several additional steps need to be performed to ensure reproducible manufacturing of the product, stability of the cargo, biodistribution, dosing, immunogenicity and long-term safety.

8. Methodological barriers, standardisation, and future directions

Pre-analytical and analytical choices continue to be a critical part of EV biomarker studies. The abundance and cargo of EVs can vary depending on blood collection tubes, centrifugation, removal of any filters, and storage temperature, as well as other factors, such as platelet contamination and freeze-thaw cycles (Coumans *et al.*, 2017). Ultracentrifugation, size-exclusion chromatography, precipitation and immunoaffinity enrich different, but overlapping populations. So, sometimes apparently contradictory results may be due to methodology instead of biology.

Characterisation is also significant. Particle size is not sufficient to determine EV identity, and particle concentration, markers necessary for the membrane and protein contamination/derinsing methods used for EV isolation and detection is suggested as part of the studies. Another significant issue is normalisation, which can dramatically change results in the case of miRNAs due to haemolysis, urinary concentration, extraction effectiveness as well as the kind of reference RNA used. Before the translation of biomarkers to a multi-centre setting is realistic, standardised reporting is necessary.

Future prospective study cohorts, with sufficient power for the outcome measures and independently validated, should be studied. Sampling should be longitudinal and synchronous in respect of important surgical events and not pre and postoperative. EV phenotype, cargo and conventional clinical variables should be put together into models and tested for discrimination, calibration and clinical utility.

Another priority is biological attribution. EV surface markers, cell defined protein markers, transcriptomic methods or tissue-of-origin technologies might help to find and differentiate the signals from kidney, endothelial, immune, platelet and parenchymal cells. Eventually, single-vesicle and spatial measurements could yield a much more accurate picture than bulk EV measurements. Doubling the efforts to understand the role of bacterial extracellular vesicles and host-microbiome EV communication, especially in postoperative delirium and infection, is warranted considering recent results of a prospective study showing that a profile of circulating bacterial EVs might hold prognostic information ([A prospective cohort study, 2025](#)).

9. Conclusion

Cells and tissues communicate via extracellular vesicles and the miRNA they carry, offering a unified biological context to understand the mechanisms of communication of surgical tissue injury between cell and organ. Their protected molecular information makes them appealing for use in liquid biopsy in the perioperative period to detect molecular information while their capacity to change behaviour of recipient-cells has potential for their role as mediators of inflammation, organ injury and repair. Current evidence exists mostly for cardiac-surgery AKI, septic shock after surgery and neurological complications after surgery; however, the translational phase is still in an early stage. Careful standardisation, serial sampling, external validation and transition to multimodal signatures with mechanistic basis are all important to the future of EV-miRNA research. With the development of solutions to these challenges, EV profiling may transition from exploratory biomarker technology into a meaningful, clinical tool for predicting injury to tracking recovery and the discovery of new therapeutic targets.

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