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Assessing vascular barrier permeability in critically ill patients: what are we really measuring?

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Abstract

Background Perturbation of vascular barrier permeability is a central mechanism in the pathophysiology of critical illness, contributing to tissue edema, impaired oxygen diffusion, and organ dysfunction. Despite advances in the field, direct bedside assessment of vascular permeability remains unavailable. Current approaches rely on indirect and compartment-specific surrogates, raising important questions about what is actually being measured.

Main body This narrative review summarizes the physiological principles underlying vascular barrier function and its disruption in conditions such as sepsis, acute respiratory distress syndrome, and major surgery. Currently available bedside tools used to assess vascular permeability or its consequences are critically appraised, including clinical examination, ultrasonography, transpulmonary thermodilution, bioelectrical impedance analysis, circulating biomarkers of endothelial injury (e.g., glycocalyx degradation products, angiopoietin-2), and albumin kinetics–based methods. While these techniques provide valuable insights, they predominantly reflect downstream consequences such as tissue edema, intravascular volume shifts, or endothelial activation rather than permeability itself. In addition, vascular permeability is a dynamic, context-dependent, and organ-specific process influenced by inflammatory, hemodynamic, and therapeutic factors, further complicating its interpretation. Each method therefore captures only a partial dimension of vascular barrier dysfunction, with important limitations related to specificity, feasibility, validation and standardization.

Conclusions No single bedside tool currently provides a comprehensive assessment of vascular permeability in critically ill patients. A multimodal approach integrating clinical evaluation, imaging, hemodynamic monitoring, and biomarkers is required to better characterize vascular barrier dysfunction. Future research should focus on validating composite indices and developing reliable, real-time bedside tools capable of directly assessing vascular permeability, with the ultimate goal of improving risk stratification and guiding personalized therapeutic strategies.

Keywords Vascular permeability, Endothelial barrier, Capillary leak syndrome, Bedside monitoring, Microcirculation, Albumin kinetics, Plasma volume, Biomarkers

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Introduction

The cardiovascular system maintains homeostasis by ensuring tissue perfusion, oxygen delivery, and metabolic exchange. While the macrocirculation regulates blood flow and perfusion pressure, the microcirculation enables exchanges between blood and tissues through a tightly regulated vascular barrier composed of the glycocalyx, endothelial cells, intercellular junctions, and basement membrane [1, 2].

The main reasons for intensive care unit (ICU) admission, i.e.sepsis, acute respiratory distress syndrome, trauma, ischemia–reperfusion injury, or major surgery often feature increased vascular permeability [2, 3]. Inflammatory and hemodynamic insults activate the endothelium, degrade the glycocalyx, and may disrupt intercellular junctions, leading to protein-rich plasma leakage into tissues. The resulting edema hinders oxygen diffusion, disrupts metabolism, and contributes to organ failure, a process often referred to as capillary leak syndrome (CLS) [4].

Despite major advances in our understanding of fluid exchange, bedside assessment of vascular permeability remains challenging. No validated tool directly measures permeability in humans, and current approaches rely on indirect indicators such as edema, plasma volume changes, and circulating biomarkers. Moreover, fluid shifts vary across organs and clinical conditions, and classical models such as the Starling principle only partially explain these phenomena in critical illness [5]. Vascular permeability should therefore be considered a dynamic and multidimensional process requiring integration of clinical examination, imaging, hemodynamics, biomarkers, and emerging technologies.

In this narrative review, we aimed to (i) summarize the key physiological principles underlying vascular barrier permeability in normal conditions and disease (except brain edema and blood–brain barrier permeability), (ii) appraise currently available bedside tools used to assess vascular permeability or its consequences in critically ill patients, and (iii) discuss the strengths, limitations, and clinical relevance of a multimodal assessment strategy.

Methods

This narrative review is based on a structured search of the PubMed/MEDLINE database. This approach does not constitute a formal systematic review, but aims to provide transparent and reproducible overview of the literature. MeSH terms and free-text combinations including "vascular permeability", "endothelial barrier", "capillary leak", "glycocalyx", "critical illness", "intensive care", "sepsis", and related expressions were used to identify relevant human and experimental studies published between January 2000 and March 2026, complemented by selected landmark articles from earlier decades. Reference lists of key papers and prior reviews were screened to capture additional publications. Studies were selected based to their relevance to mechanisms of vascular barrier injury, available bedside assessment techniques and implications for fluid management.

Vascular barrier permeability: from physiology to pathology

Defining "vascular permeability" is challenging because the term encompasses both the biophysical properties of the endothelial barrier and their clinical consequences. Strictly, permeability is determined by hydraulic conductivity (Lp) and the reflection coefficient (σ) within the revised Starling framework [5, 6]. However, no universal clinical definition exists, and these parameters cannot be measured directly at the bedside. Consequently, vascular permeability is often used clinically as an "umbrella term" describing the processes governing transvascular and trans-endothelial fluid exchange and their consequences.

Trans-endothelial flux

Under physiological conditions, endothelial integrity is tightly regulated. Of note, vascular permeability varies across organs (Fig. 1). Trans-endothelial fluid and solute flux is determined by the interaction between barrier properties and Starling forces; in the revised Starling model, the glycocalyx and protein-poor subglycocalyx space form the main oncotic barrier, with minimal steady-state capillary reabsorption and most filtered fluid returning via the lymphatic system [5, 7]. Accordingly, increased vascular permeability reflects changes in Lp and/or the σ that enhance transcapillary flux for a given pressure gradient.

Inflammatory conditions and increased permeability

Under normal conditions, vascular permeability to large molecules (> 60-70 kDa) is limited, reflecting tight intercellular junctions, an intact glycocalyx and a relatively high σ for plasma proteins. Inflammatory mediators, ischemia–reperfusion injury and mechanical stress can profoundly alter this balance, with increases in Lp and reductions in σ that facilitate the passage of protein-rich fluid into the interstitium. The principal mechanisms underlying this enhanced permeability are the alterations in hydrostatic pressures, shedding of endothelial glycocalyx components, disassembly of adherens and tight junctions, and ultimately, cytoskeletal contraction with formation of inter-endothelial gaps. These structural changes convert a highly selective barrier into a more leaky interface, blunting the transcapillary oncotic gradient and predisposing to tissue edema when compensatory mechanisms are exceeded [8, 9].

Role of hydrostatic, oncotic and interstitial fluid pressures

Capillary hydrostatic pressure (Pc) is a central determinant of transcapillary fluid exchange and lies between arteriolar (Pa) and venular (Pv) pressures. According to the Pappenheimer–Soto Rivera relationship, Pc is more sensitive to changes in Pv than Pa, making venous pressure a critical regulator of filtration in many vascular beds [10]. An increase in Pv raises Pc and therefore enhances fluid movement into the interstitium, especially when hydraulic conductivity (Lp) is high. Under normal endothelial conditions, this predominantly results in water flux that is limited by the colloid osmotic pressure gradient and the barrier function of the glycocalyx, while the excess filtered fluid is removed by lymphatic drainage. When vascular permeability is increased—i.e. when Lp rises and the reflection coefficient for proteins (σ) falls—an elevation in Pc drives not only water but also protein-rich plasma across the endothelial surface layer. Thus, hydrostatic and oncotic pressures modulate the level of vascular barrier dysfunction but do not fully determine it [11].

In addition, interstitial fluid pressure (Pif), normally around −2 to −3 mmHg, may decrease to −7.5 to −10 mmHg during inflammation, thereby enhancing the suction effect of the interstitium and fluid filtration [12, 13]. Interstitial forces also contribute, as inflammation-induced reductions in interstitial pressure may further promote fluid extravasation.

Role of lymphatic flow

Beyond the endothelial barrier itself, lymphatic drainage is a key determinant of how changes in permeability translate into clinically apparent edema. When transcapillary filtration increases, lymph flow can rise by an order of magnitude and delay interstitial fluid accumulation, as described by Guyton's concept of "interstitial washdown", whereby increased lymph flow dilutes interstitial proteins and partially restores the oncotic gradient [14]. More recent models of capillary–lymphatic interaction confirm that filtration occurs along most of the capillary length and that effective lymphatic drainage is essential to maintain plasma–interstitial fluid balance. In inflammatory states, however, cytokine-induced changes in extracellular matrix composition, interstitial compliance and pressure, together with potential lymphatic dysfunction, may reduce this compensatory reserve, so that a given increase in Lp or fall in σ more readily results in tissue edema and organ dysfunction [15].

Organ-specific microvasculature

Organ-specific microvascular architecture critically determines baseline permeability and susceptibility to edema. Continuous capillaries (muscle/skin) limit macromolecular flux, whereas fenestrated (kidney/endocrine) and sinusoidal (liver) beds permit greater protein and fluid passage. Under inflammatory or hemodynamic stress, these structural differences translate into distinct, organ-specific patterns of capillary leak (Fig. 1). The detailed discussion of phenomena occurring in each organ falls beyond the scope of this review.

The distribution and subsequent fate of administered fluids

After intravenous administration, crystalloids initially expand the plasma volume before rapidly redistributing across the capillary wall into the interstitial space, with most equilibration occurring within 30–40 min in healthy individuals [13, 16]. Under physiological conditions, this extravasated fluid enters a rapidly exchanging interstitial compartment and is efficiently cleared by the

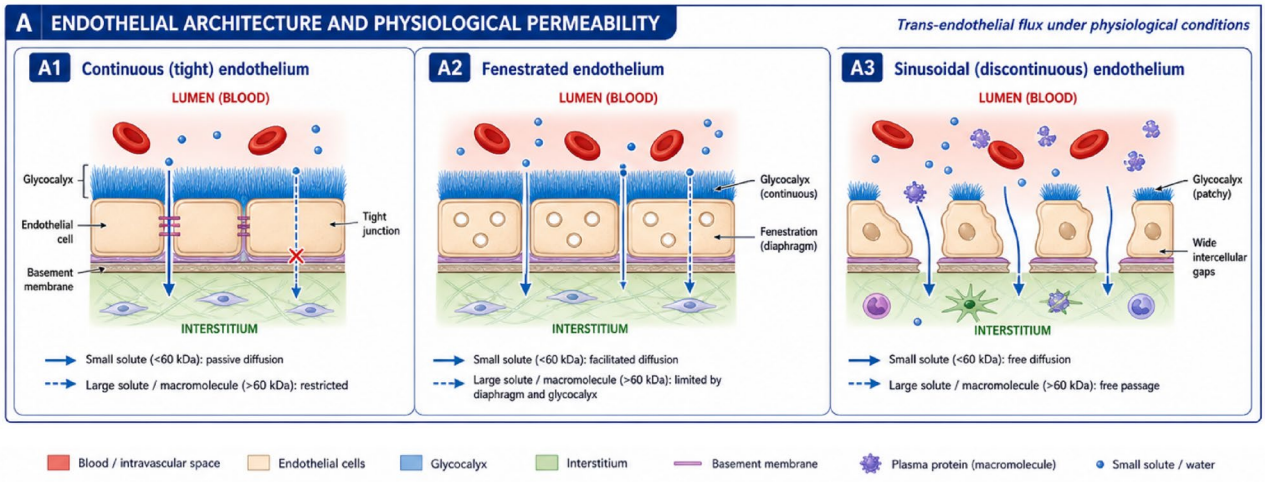


Fig. 1A Organ-specific microvascular architecture and context-dependent vascular permeability. Accordingly: (**A**) Organ-specific microvascular architectur

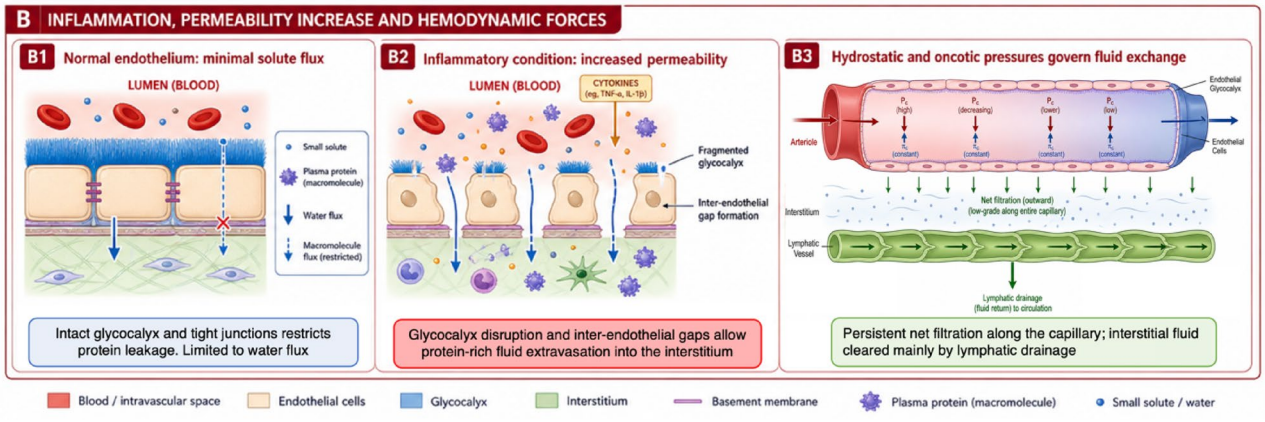


Fig. 1B (**B**) Context-dependent vascular permeability

lymphatic system, which increases its flow in response to enhanced filtration and thereby limits edema formation while maintaining plasma volume and protein homeostasis. During large-volume fluid administration, however, rising interstitial hydrostatic pressure progressively offsets the normal sub atmospheric interstitial pressure, markedly increasing tissue compliance and allowing excess fluid to accumulate in a slowly equilibrating interstitial compartment, often referred to as the "third space" [17]. In inflammatory states, fluid redistribution is governed by a different mechanism: cytokine-mediated disruption of fibroblast–matrix interactions generates a profoundly negative interstitial pressure that actively draws fluid from the vascular compartment into the interstitium, while concomitant impairment of intrinsic lymphatic pumping limits its return to the circulation. Consequently, the persistence of edema in critical illness is determined not only by increased vascular permeability but also by the balance between interstitial pressure and lymphatic drainage, explaining how hypovolemia, hypoalbuminemia, and tissue edema can coexist despite ongoing fluid administration [12, 13].

How to assess vascular permeability at the bedside?

Bedside approaches are classified according to what they actually measure in relation to the vascular barrier, distinguishing three complementary distinct information levels: (i) the tools that describe the global clinical phenotype of fluid accumulation, (ii) the techniques that quantify fluid redistribution across compartments, and (iii) the methods that more directly explore endothelial barrier injury and macromolecular leakage. These various techniques are detailed below and summarized in Table 1.

Level 1 : Global clinical phenotype of fluid accumulation

Level 1 tools provide a rapid, widely available way to recognize the clinical phenotype of suspected capillary leak, but they remain nonspecific and do not discriminate increased vascular permeability from other causes of fluid accumulation.

Back to basics: clinical assessment

Clinically, the consequences of vascular hyperpermeability are frequently observed in critically ill patients and are typically described as the Capillary Leak Syndrome (CLS). CLS is defined by the combination of generalized edema, positive fluid balance and weight gain despite hemodynamic instability, and relative hypovolemia [18]. Both the occurrence of CLS and a positive fluid balance in the ICU are associated with adverse outcomes [19]. However, positive fluid balance and edema formation are not specific for increased vascular permeability and may also reflect alternative mechanisms such as decreased oncotic pressure, excessive fluid administration in the setting of renal failure, or venous congestion. Moreover, bedside assessment of edema (most commonly through pitting edema grading or limb circumference measurement) remains subjective, static, and insensitive to short-term changes. While ICU bed scales provide continuous weight estimates, their accuracy and precision over days remain subject to measurement variability and confounding factors [20]. As such, clinical examination and body weight alone cannot reliably quantify fluid accumulation and should be interpreted as an initial screening step within a broader multimodal evaluation.

Ultrasonography related techniques

Bedside ultrasound has emerged as a rapid, reliable, and non-invasive technique that enables both functional and

Table 1 Bedside assessment methods of vascular permeability

Technique	Primary dimension explored	ICU data / validation	Typical range / pattern	Main strengths	Main limitations / current role
Level 1: Global clinical phenotype of fluid accumulation					
Clinical assessment	Global clinical consequences of fluid extravasation	ICU patients, postoperative, sepsis Routine ICU use; limited formal validation	Not applicable	Universal, free, continuous trend	Nonspecific, subjective and static
Lung ultrasound (B-Lines)	Pulmonary interstitial/alveolar edema	ARDS, sepsis, heart failure Prognostic associations	B-lines score : 0 to 32 (0 to 8, 4 zones) [22]	Non-invasive, bedside, structural and functional insights	Indirect, observer-dependent, difficult to interpret in ARDS/pneumonia
Skin/subcutaneous ultrasound	Peripheral interstitial fluid accumulation	ICU/postoperative studies	Semi-quantitative grading (1–4) [28]	Non-invasive, repeatable	Indirect, regional assessment only
Level 2: Quantification of fluid redistribution between compartments					
Bioelectric Impedance Analysis	Electrical tissue conductivity, ECW/TBW, Kf	Post-surgery, sepsis, ICU patients Associations with overload and outcomes	ECW/TBW ≥ 0.4 if fluid overload [33]	Non-invasive, dynamic fluid monitoring	Indirect measure, accuracy debated, algorithm dependent
Transpulmonary Thermodilution (EVLW, PVPI)	Pulmonary edema and permeability	Well validated in ARDS and sepsis	EVLW > 10 mL/kg; PVPI > 3 if pulmonary vascular leakage [30]	Semi-invasive, quantitative, correlates with outcomes	Systemic permeability not assessed, invasive
ePVS	Intravascular plasma volume / congestion	Sepsis, COVID-19 ARDS, heart failure cohorts	ePVS ≈ 4–5 dL/g (stable); higher values in congestion/sepsis (> 7dL/g) [41]	Cheap, uses routine labs; tracks congestion	Affected by anemia/transfusion/, not a permeability measure
Vascular Leak Index (VLI)	Tendency of infused fluids to leave circulation	Large sepsis dataset	Higher quartiles associated with mortality [45]	Quantitative, correlates with outcomes	Requires accurate input, influenced by vasodilation/constriction, not prospectively validated
Initial distribution volume of glucose (IDGV)	Functional extracellular fluid space	Sepsis, cardiac surgery, burns, pediatrics, ARDS, myocardial infarction cohorts Repeatability shown but limited outcome data	Normal values:~110–130 mL/kg, higher in overload [46,47]	Simple bolus technique, cost-effective, dynamic	Reflects volume distribution, not permeability requires serial glucose sampling; largely research/supportive tool
Hyperspectral Imaging (TWI)	Tissue water and oxygenation	Sepsis, surgery	Indices expressed on arbitrary scale (0–100) [48,50], no cut-off	Non-invasive, detailed water/oxygenation maps, real-time	Few studies, mainly research setting, high cost
Venous Congestion plethysmography (Kf)	Capillary filtration coefficient of peripheral microvasculature	Few small human studies in cardiovascular disease and sepsis; no ICU outcome validation	Kf ~ 2–4 mL/min/100 mL tissue (healthy) [51]	Non-invasive, dynamic	Technically demanding; lack of standardized protocols and cut-offs; research-only at present
Bronchoalveolar Lavage Fluid (BALF)	Alveolar-capillary permeability	ARDS	BALF protein highly variable; no normal range	Direct alveolar-capillary assessment	Invasive, limited to pulmonary compartment
Level 3: Endothelial barrier–oriented and macromolecular leakage approaches					
Level 3 A : Structural endothelial and glycocalyx injury markers					
Glycocalyx biomarkers (Syndecan-1, Glycosaminoglycans)	Glycocalyx and endothelial layer injury	Sepsis, trauma, ischemia-reperfusion cohorts; consistent outcome associations	Syndecan-1: ~20–40 ng/mL (healthy); >200 ng/mL in sepsis [55]	Severity marker of vascular injury, prognostic	Mechanisms unclear, not specific of permeability, assay heterogeneity, research-supportive
Intercellular Junction Markers (VE-cadherin, ZO-1, occludins	Junctional disruption	Small mechanistic ICU studies	Broad interstudy variability, No validated cut-off	Mechanistic endothelial markers; not linked directly to fluid load	Exploratory; not linked to bedside decisions

Table 1 (continued)

Technique	Primary dimension explored	ICU data / validation	Typical range / pattern	Main strengths	Main limitations / current role
Angiopoietins (Ang-1/2)	Angiopoietin-1 receptor-mediated endothelial instability, systemic endothelial activation	Sepsis, ARDS, cardiopulmonary bypass cohorts; strong prognostic signal	Ang-2:~1–3 ng/mL (healthy); >5–10 ng/mL in sepsis [68]	Integrates endothelial activation; outcome associations	No interventional validation, influenced by coagulopathy
Level 3B: Albumin and macromolecular leakage indices					
Radio-labeled albumin (^{125}I-Albumin, ^{99}mTc-Albumin)	Absolute plasma volume, albumin kinetics	Healthy subjects, cirrhosis, ICU patients; robust physiologic validation; few modern ICU studies	Normal values: Men: ~40–45 mL/kg; women: ~38–42 mL/kg [71]	Direct measurement of PV; ^{99}mTc has lower radiation, allows serial measurements, reference methods	Radiation, impractical bedside, high cost, limited availability (nuclear medicine required);
Non-labeled albumin dilution technique	Plasma volume after albumin bolus	Pilot study in ICU patients	Comparable but wider dispersion than isotope methods	Simple, rapid bedside estimation	Less accurate than isotope
Transcapillary escape rate (TER) of albumin	Macromolecular vascular permeability	Small sepsis and perioperative cohorts (surgical trauma, cardiac surgery)	~5%/h (healthy); higher in inflammation [17]	Sensitive marker of endothelial dysfunction and vascular permeability	Protocol-dependent, influenced by plasma volume changes, and does not account for lymphatic return; requires isotopes, no outcome-guided use
BVA-100 device (semi-automated radiolabeled albumin tool)	Absolute blood/plasma volume and red cell volume	Validated against isotope reference methods; outcome-oriented HF/dialysis studies, very limited ICU data	Similar to isotope PV ranges [74]	Highly accurate, FDA-cleared PV/BV quantification; can guide decongestion	Requires radiolabeled albumin and dedicated analyzer; logistics and cost; requires more validation in ICU
Net Albumin Leakage (NAL)	Net interstitial albumin accumulation	Proof of concept major abdominal surgery, and sepsis studies	Near zero in steady state; positive in inflammation [80]	Accounts for lymphatic return; no isotopes; reflects dynamic leakage	PV estimation error (≥ 10%); limited ICU validation, needs larger studies
Level 3 C: Microcirculatory and endothelial surface layer assessments					
Microcirculatory Analysis (TVD, PVD, PPV…)	Microcirculation, perfusion consequences of edema	Multiple sepsis and shock cohorts; outcome associations	PPV ~ 90–100% (healthy); ↓ in shock	Bedside, precision direct microvascular assessment	Indirect, technical skill required, limited standardization, high cost
Perfused boundary region (PBR)	Glycocalyx thickness, depth of red blood cells penetration	ICU sepsis and critical illness cohorts; associated with severity and mortality	≈ 1.7–2.0 µm in healthy; ↑ in sepsis (PBR ≥ 2.5 µm, no validated threshold	Bedside, non-invasive index of glycocalyx injury integrated with microcirculation imaging	Requires dedicated software; inter-observer and inter-study variability; research/expert-center tool

ARDS: Acute respiratory distress syndrome; BALF: Bronchoalveolar Lavage Fluid ; PV: plasma volume; ePVS: estimated plasma volume status; ECW: extracellular water; IDGV : Initial distribution volume of glucose; ICU: intensive care unit; NAL: Net Albumin Leakage; TBW: total body water; EVLW: extravascular lung water; PBR: perfused boundary region; PVPI: pulmonary vascular permeability index; TER: transcapillary escape rate; TVD total vessel density; PVD: perfused vessel density; PPV: proportion of perfused vessels; TWI: Tissue Water Index. Reported ranges are derived from healthy volunteers or selected clinical cohorts and should not be interpreted as diagnostic thresholds. For most techniques, no validated clinical cut-off values exist

structural assessment of multiple organs, particularly the skin and lungs, which are among the most affected by CLS and edema [21].

Lung ultrasound provides accurate bedside assessment of extravascular lung water (EVLW) in ICU patients through the visualization of B-lines, with strong correlation to transpulmonary thermodilution measurements (r^2 = 0.68–0.92) [22, 23]. These vertical artifacts result from acoustic reverberations generated at the air–fluid interface between collapsed, fluid-filled, and aerated alveoli reflecting the presence of interstitial or alveolar edema [24]. B-line artifacts demonstrate high diagnostic accuracy as a marker of increased EVLW, with sensitivities and specificities exceeding 90% when compared to chest computed tomography or transpulmonary thermodilution [25].

In parallel, soft-tissue and subcutaneous ultrasound has recently emerged as a complementary method for evaluating peripheral edema. It has long been used in the diagnosis and follow-up of chronic or inflammatory disorders involving the skin, such as systemic sclerosis or lymphedema [26, 27]. More recently, this approach had been evaluated in critically ill patients, grading subcutaneous edema on a four-point scale across seven body regions. Edema was most frequently observed in the abdominal wall and showed a clear dependence on gravitational distribution in this cohort [28]. To date, no evidence demonstrates its superiority over clinical assessment using pitting edema grading.

Ultrasound can also characterize systemic venous congestion. The Venous Excess Ultrasound Score (VExUS) combines inferior vena cava and abdominal venous Doppler patterns to grade venous hypertension and has been associated with fluid overload and acute kidney injury in ICU patients [29]. Because venous congestion may promote edema via increased venous and capillary hydrostatic pressure independently of endothelial permeability, VExUS represents a useful complementary tool for assessing fluid overload.

Overall, ultrasonography provides valuable organ-specific information on fluid extravasation and redistribution. Ultrasound therefore quantifies the consequences of permeability changes and congestion, rather than capillary permeability itself, but remains a cornerstone of bedside assessment when integrated with clinical and hemodynamic data.

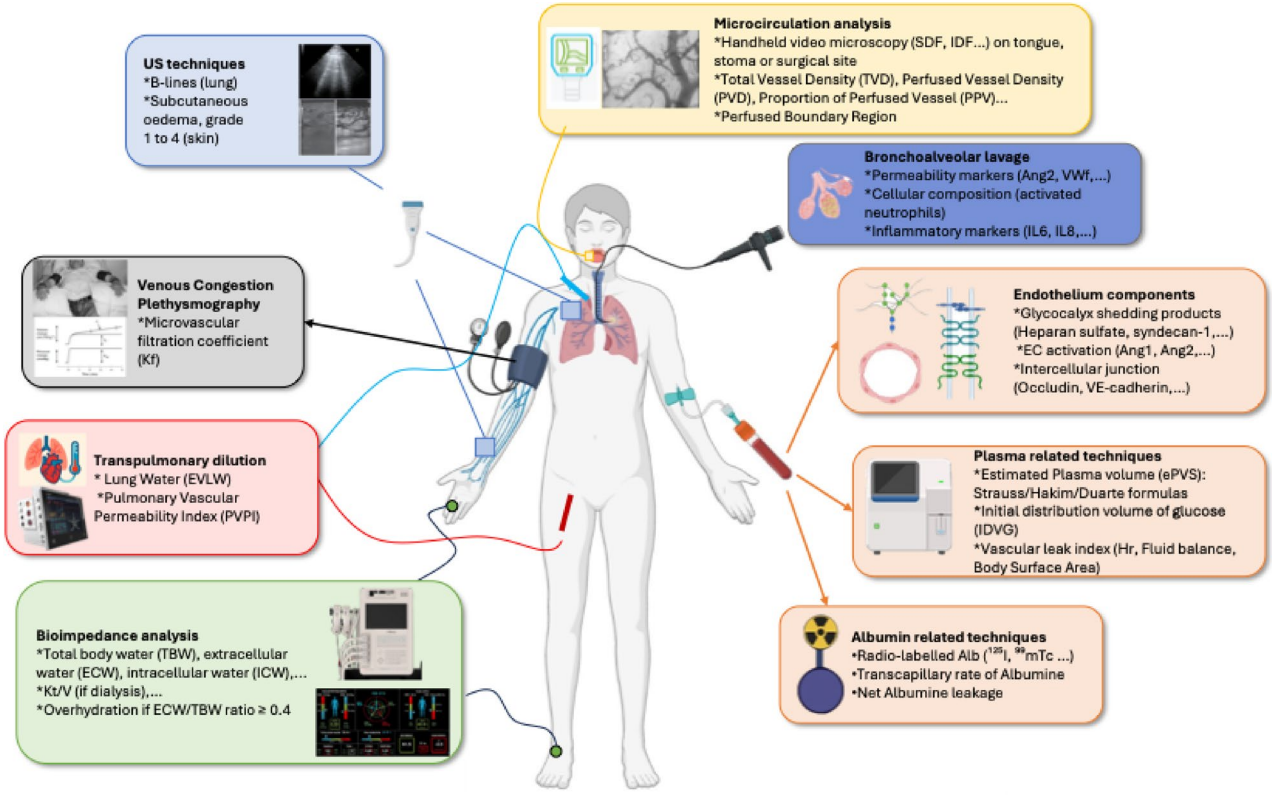


Fig. 2 Overview of methods available for assessing vascular permeability in critically ill patients. Schematic overview of bedside and advanced techniques used to evaluate vascular barrier dysfunction, highlighting their complementary and compartment-specific contributions to the assessment of vascular permeability

Table 2 Formulas used to estimate plasma volume and vascular or albumin leakage in critical care

Plasma volume status estimation and surrogates related formulas					
Description	Formulas	Main compartment explored	Practical implementation		**Comments**
ΔePVS [43]	$\Delta\, ePVS = 100\ \times\ \frac{hemoglobin\ (g/dL)\ (before)}{hemoglobin\ (after)} \times\ \frac{100 - Hct\ (\%)\ (after)}{100 - Hct\ (\%)\ (before)} - 100$	Intravascular	Routine Hb/Hct values, serial blood samples		Estimates relative changes in plasma volume over time based on hemodilution or hemoconcentration. Reflects intravascular consequences of fluid shifts.
Actual/Ideal PV [88]	$\frac{actual PV = (100 - hematocrit(\%))/100 \times\ (a + (b \times\ dry\ weight\ (kg))}{ideal PV = c\ \times\ dry\ weight\ (kg)}$	Intravascular	Single calculation from Hct and anthropometric (males: a = 1530, b = 41, c = 39 / female: a = 864, b = 47.9, c = 40).		Estimates absolute plasma volume relative to an expected ideal value. Explores intravascular volume status only.
Vascular leakage index [45]	$VLI = \frac{\Delta\, Hct\ (\%)}{Net\ Fluid\ Balance\ (L)} \times\ Body\ surface\ area\ (m2) \times\ 1000$	Global	Requires Hct and accurate fluid balance data; applicable in most ICUs but dependent on fluid balance data quality ΔHct=percentage change in hematocrit. Net Fluid Balance=difference between fluid intake and output over the same period		Estimates the tendency of administered fluids to leave the circulation. Reflects the global impact of vascular leak rather than endothelial permeability itself. .
Albumin based techniques related formulas					
Radio-labeled albumin techniques	$PV = \frac{Radioactivity\ of\ standard\ \left(\frac{cpm}{ml}\right) \times\ dilution\ of\ standard \times\ volume\ injected\ (mL)}{Radioactivity\ of\ postinjection\ sample\ \left(cpm/mL,\ adjusted\ to\ \mathrm{T}^0\right)}$	Intravascular	Requires exogenous radio-labelled albumin, dedicated counting equipment and repeated blood samples, Research tools, not suitable for routine bedside assessment.		Reference methods for absolute plasma volume and albumin kinetics. Cpm is the count per minutes
Non radio-labelled albumin formula [72]	$PV = \frac{bolus(\mathrm{g})}{PAlb1 \times\ \left(\frac{Hct0}{Hct1}\right) - PAlb0}$	Intravascular	Required a standardized bolus of 20% albumin (200mL, 40 g) and serial Hct/albumin measurement. No radioactivity but careful timing and lab support		More feasible than radio-labelled techniques but still not widely used in routine practice.

Albumin based techniques related formulas				
Transcapillary escape rate of Albumin [76]	$TER\ (\%/h) = \frac{\ln(A_0) - \ln(A_t)}{\Delta t}$ x100	Intravascular → interstitial	IV bolus of radioiodine-labeled albumin; venous blood sampling over 60–90 min; plasma radioactivity measured by gamma counting; TERalb calculated as percentage decline in plasma tracer activity per hour using a mono-exponential model.	Where A_0 and A_t are the plasma radioactivity (counts per minute [cpm]) measured immediately after equilibration and at time t, respectively, and t is expressed in hours
Net albumin leakage [78]	$IAM = PV \times PAlb$ Where $PV = 1 - (Hct \times 0.91) \times \mathrm{BV}$ And $BV = a \times height^3\ (m) + b \times weight\ (kg) + c\ (for\ male)$ $IAM' = albumin\ gain - albumin\ loss$ $Albumin\ gain = (plasma\ tranfusion\ volume \times plasma\ albumine\ concentration) + (platelets\ transfusion\ volume \times \text{platelet albumine concentration}) + (\text{albumin infusion concentration} \times \text{albumin volume})$ $Albumin\ loss = (bleeding\ volume \times mean\ PAlb \times (1 - Hct)) + (\text{urinary albumin concentration} \times \text{urine volume}) + (\text{drain albumin concentration} \times \text{drain fluid volume})$ $NAL = IAM' - IAM$	Interstitial	Required detailed tracking of all albumin input and output plus serial plasma albumin and Hct, may need drain and urine sampling. Complex calculations, methodology demanding, difficult to apply for routine bedside use. (males: a = 0.3669, b = 0.03219, c = 0.6041; female: a = 0.3561, b = 0.03308, c = 0.1822)	Estimates net interstitial albumin accumulation by integrating albumin gains and losses over time. Reflects severe vascular barrier dysfunction. The f-ratio 0.91 represents the ratio between total body hematocrit and large vessel blood Hct.

ePVS: estimated plasma volume status, Hct: hematocrit, PAlb: plasma albumin, PV: plasma volume, BV: blood volume, IAM: intravascular albumin mass, NAL: net albumin leakage, TER: transcapillary escape rate

Level 2 – Quantification of fluid redistribution between compartments

Level 2 techniques add granularity by quantifying how and where fluid redistributes between compartments, yet they still mainly capture the consequences of barrier dysfunction and cannot, on their own, distinguish increased permeability from venous congestion or hypo-oncotic states. Although several of these techniques are relatively accessible, their bedside use remains limited outside academic centers (Tables 2 and 3).

Transpulmonary Thermodilution and Extravascular Lung Water

Transpulmonary thermodilution provides semi-invasive, multiparametric hemodynamic monitoring and enables estimation of EVLW. EVLW reflects the accumulation of fluid within the pulmonary interstitium and alveoli and is strongly associated with mortality in critically ill patients, irrespective of the presence of acute respiratory distress syndrome (ARDS) [30, 31].

The Pulmonary Vascular Permeability Index (PVPI) can help differentiate whether elevated EVLW (> 10 ml/kg) is due to increased permeability, as indicated by a high PVPI value (> 3). PVPI is increased in patients with ARDS, compared with cardiogenic edema and pleural effusion with atelectasis patients [32]. Thus, in ARDS, a PVPI > 3 indicates a severe pulmonary endothelial injury with a likely increased pulmonary vascular barrier permeability. Although PVPI reflects pulmonary microvascular permeability, its interpretation remains lung-specific and should not be extrapolated to systemic vascular leakage.

Bioelectric impedance analysis

Bioelectrical impedance analysis (BIA) is a non-invasive technique that estimates body fluid compartments based on tissue electrical conductivity. BIA provides measurements of total body water (TBW), extracellular water (ECW), and intracellular water, allowing estimation of fluid overload [33]. More recent devices are also able to differentiate intravascular and extravascular fluid compartments, and can measure Kt/V during hemodialysis [33]. An ECW/TBW ratio ≥ 0.4 has been proposed as an indicator of fluid overload. In the ICU, an elevated ECW/TBW ratio has been correlated with higher mortality and an increased incidence of organ dysfunction, including the need for mechanical ventilation and acute kidney injury [34, 35]. Beyond changes in TBW and ECW, intracellular water may progressively decrease during crystalloid resuscitation [36]. This intracellular dehydration, shifting water into the interstitial space, is not captured by most bedside "permeability" markers and supports interpreting BIA findings within a three-compartment framework [37].

BIA offers the advantages of simplicity, repeatability, and whole-body assessment. However, it does not distinguish between mechanisms of fluid accumulation and remains an indirect marker of vascular permeability. Its accuracy may also be affected by rapid fluid shifts, altered tissue composition, and patient positioning.

Insights from bronchoalveolar lavage fluid analysis

Analysis of bronchoalveolar lavage fluid (BALF) provides direct insight into the integrity of the alveolar–capillary barrier and remains a reference approach for characterizing pulmonary vascular permeability in ARDS. Elevated protein concentrations in BALF, increased BALF-to-plasma protein ratios, and enrichment in inflammatory mediators reflect enhanced permeability of the alveolar–capillary membrane and loss of barrier selectivity [38]. In addition, the cellular composition of BALF—particularly the presence of activated neutrophils and increased concentrations of pro-inflammatory cytokines such as IL-6 and IL-8, although no validated clinical cut-off values exist—further indicates ongoing lung injury and amplification of vascular barrier dysfunction [39].

Importantly, BALF assessment is inherently lung-specific and invasive, requiring bronchoscopy and standardized conditions. Its use is therefore restricted to selected patients and research settings and does not allow dynamic bedside monitoring. As such, BALF analysis should be viewed as a complementary reference tool that informs pathophysiological understanding of pulmonary permeability rather than as a routine bedside assessment method.

Estimated plasma volume status

Estimated plasma volume status (ePVS) is derived from routine hemoglobin and hematocrit measurements using validated formulas (Table 2). Compared with isotope-based reference methods, ePVS shows moderate to good correlation with measured plasma volume across different clinical settings [40]. Elevated ePVS has been associated with worse outcomes across multiple clinical settings [41, 42]. Serial changes in ePVS are more informative than isolated measurements, particularly during fluid administration or deresuscitation, as they reflect shifts in intravascular volume [43, 44]. Although ePVS is a simple, non-invasive, cost-effective tool, it remains an indirect marker influenced by hemodilution or hemoconcentration, bleeding, hemolysis, and transfusion. Consequently, it is better interpreted as a marker of congestion or global fluid accumulation than as a direct measure of vascular permeability.

Vascular leak index (VLI)

A novel index was recently proposed to assess vascular permeability in sepsis, termed the VLI, which is derived

from blood volume and hematocrit measurements (Table 2). Higher VLI values, reflecting greater fluid accumulation, is associated with increased in-hospital mortality [45]. Despite its rationale, VLI remains sensitive to inaccuracies in fluid balance recording and hematocrit modifications. Moreover, changes in vascular tone, vasopressor use, or red blood cell transfusion may influence its calculation. Consequently, VLI should be viewed as a prognostic index reflecting the global impact of vascular leak rather than as a direct measure of permeability.

Initial distribution volume of glucose (IDVG)

The IDVG is derived from the early decline in plasma glucose following a small intravenous glucose bolus and reflects the rapidly accessible extracellular fluid space during the first 3 min. Although increased IDVG has been reported in conditions associated with capillary leak, such as sepsis, burns, and major surgery, it remains an indirect and controversial measure. Accordingly, this parameter is best viewed as a marker of global fluid redistribution rather than a direct measure of intravascular volume or vascular permeability [46, 47].

Hyperspectral imaging (HSI)

HSI is a noninvasive optical imaging technique that provides spatially resolved information on tissue oxygenation, hemoglobin content, and tissue water index based on wavelength-specific light absorption and reflection. With a resolution of 5 nm, each pixel is analyzed across specific wavelengths with results expressed in an arbitrary scale from 0 to 100. Combined with machine learning algorithms, it can process and analyze different tissue types or changes.

In critically ill patients, HSI-derived indices have revealed patterns consistent with impaired microcirculation and increased tissue water content in sepsis and major surgery [48–50]. However, HSI-derived parameters remain semi-quantitative and are expressed on arbitrary scales, with no validated clinical cut-off values. Importantly, HSI does not directly measure vascular permeability, and increased tissue water index may reflect multiple mechanisms beyond vascular leakage. In addition, measurements may be affected by several confounding factors, including skin properties and local hemodynamic conditions.

Venous congestion plethysmography

Venous congestion plethysmography is a noninvasive technique used to quantify microvascular fluid dynamics, including capillary permeability and transvascular fluid exchange. It works by gradually inflating a limb cuff to sub-diastolic pressures, restricting venous return while maintaining arterial inflow. The resulting venous pooling increases limb volume, which is continuously measured. Once cuff pressure exceeds the venous pressure, capillary filtration begins, reflected by a nonlinear rise in volume. The slope of this pressure-volume curve defines the microvascular filtration coefficient, a key indicator of capillary permeability [51]. While well established in cardiovascular research, its application in critical care remains limited. Further studies are required to determine its clinical relevance in ICU populations.

Level 3 - Endothelial barrier–oriented and macromolecular leakage approaches

Level 3 approaches, which assess endothelial injury, macromolecular leakage, and microvascular alterations, most closely reflect the underlying mechanisms of vascular permeability.

Level 3 A – Structural endothelial and glycocalyx injury markers

Biomarkers of glycocalyx shedding Several circulating biomarkers reflecting vascular barrier injury have been investigated, including glycocalyx degradation products, markers of intercellular junction disruption, and mediators of endothelial stability. The glycocalyx contributes to vascular barrier selectivity, and experimental studies suggest that its degradation increases transvascular fluid and solute flux [5, 52, 53].

Elevated plasma concentrations of syndecan-1, glycosaminoglycans, and hyaluronan have been reported in sepsis, trauma, and ischemia–reperfusion injury, with higher levels associated with disease severity and mortality [18, 54, 55]. Although glycocalyx damage contributes to vascular leak, particularly in sepsis [56–58], it is neither sufficient nor specific to explain increased permeability. Vascular barrier dysfunction results from injury to multiple structural components, including intercellular junctions and the basement membrane, and glycocalyx shedding alone should not be interpreted as a direct marker of permeability. In addition, glycocalyx turnover is a naturally occurring process that may be accelerated by a variety of stimuli, even relatively mild inflammatory stimuli.

Intercellular junctions' disruption Endothelial intercellular junctions play a central role in maintaining barrier integrity. Vascular endothelial cadherin is the key transmembrane component of endothelial *adherens* junctions, exclusively expressed by endothelial cells across all vascular beds [59]. Circulating soluble Vascular endothelial cadherin has emerged as a promising biomarker of vascular stress and endothelial dysfunction in a broad range of inflammatory states, including sepsis, and has been associated with organ dysfunction and mortality [18, 60,

Table 3 Implementation of vascular permeability tools according to bedside availability, level of information, validation and cost

Routine (available in many centers, easily repeatable, daily use, low to moderate cost) $	**Emerging** (expert centers, early clinical use, moderate to high cost) $$	**Research** (expert centers, research-grade techniques, high cost) $$$
Level 1: • Clinical assessment of edema and fluid balance • Lung ultrasound (B-lines) • Skin / subcutaneous ultrasound for peripheral edema	**Level 2**: • Hyperspectral imaging • Composite multimodal scores (clinical, US, limited biomarkers) • BALF protein content and fluid-to-plasma protein ratios in ARDS	**Level 2**: • Venous congestion plethysmography
Level 2: • Standard labs for ePVS / VLI (Hb, Hct, routine chemistry) • Bioelectrical impedance analysis (total / extracellular water) • Transpulmonary thermodilution (EVLW, PVPI)	**Level 3**: • Selected endothelial biomarkers (e.g. syndecan-1, angiopoetin-2) • Simple albumin kinetics (non-radio-labelled PV, NAL) • Handheld intravital videomicroscopy (including PBR)	**Level 3**: • Extended endothelial biomarker panels • Radio-labelled albumin PV and transcapillary escape rate

Practical availability of bedside tools used to assess vascular barrier dysfunction, categorized as routine, emerging or research techniques and mapped to three information levels: Level 1 (global clinical phenotype of fluid accumulation), Level 2 (quantification of fluid redistribution between compartments) and Level 3 (endothelial barrier–focused and macromolecular leakage approaches)

ePVS: estimated plasma volume status, Hb: hemoglobin; Hct: hematocrit, PV: plasma volume, NAL: net albumin leakage, EVLW: extravascular lung water: PVPI: pulmonary vascular permeability index, PBR: perfused boundary region

61]. Tight junction proteins have also been investigated as potential biomarkers of vascular barrier injury: elevated plasma concentrations of zonula occludens-1, occludin, zonulin, and claudin-5 have been described in patients with sepsis, with higher concentrations correlating with disease severity [62, 63]. Despite their mechanistic relevance and promising results in animals, junctional biomarkers have been inconsistently linked to quantitative measures of fluid accumulation or edema formation in humans. Technical limitations of current assays preclude their use as a routine biomarker.

Angiopoietins and the Tie2 axis Among circulating biomarkers, angiopoietin-2 (Ang-2) has emerged as one of the most extensively studied surrogates of vascular barrier dysfunction. Ang-2 antagonizes the stabilizing effects of angiopoietin-1 on the Tie2 receptor, promoting endothelial activation, glycocalyx degradation and junctional destabilization which have been linked to increased permeability in experimental models [64–67]. Elevated Ang-2 levels have been consistently associated with mortality in sepsis, particularly when combined with coagulopathy biomarkers and with worse outcomes in ARDS and after cardiopulmonary bypass [68–70].

Importantly, Ang-2 concentrations correlate with clinical manifestations of vascular leak, including fluid accumulation and organ dysfunction, making it a particularly attractive biomarker for risk stratification [18]. Despite the limited number of clinical studies, Ang-2 appears to be as a robust surrogate marker of vascular permeability. The Ang-1/Ang-2–Tie2 axis represents not only a promising biomarker pathway but also a potential therapeutic target in critical illness.

In summary, measurement of circulating biomarkers of vascular barrier injury are feasible bedside tools that may help identify patients at risk of increased permeability. Their value lies primarily in serial assessment rather than isolated measurements. However, interpretation remains limited by uncertain thresholds, assay variability, biomarker kinetics, and limited endothelial specificity. Consequently, these markers are best viewed as indicators of glycocalyx degradation and vascular stress rather than direct measures of vascular permeability, and their relationship with capillary leak in humans requires further investigation.

Level 3B: Albumin and macromolecular leakage indices.

Radiolabeled albumin techniques Albumin kinetics have long been used to explore vascular permeability, given albumin's central role in maintaining oncotic pressure and its restricted trans-endothelial passage under physiological conditions. Plasma volume measurement using radiolabeled albumin (^{125}I-labeled Albumin or ^{99}mTc-labeled Albumin) has historically been regarded as the reference method for quantifying intravascular volume and albumin distribution [71]. The main limitation of radioisotope techniques in the ICU lies in their restricted availability and the logistical challenges of isotope preparation, which requires access to a nuclear medicine facility.

Even if non-labeled albumin could provide a simple and rapid method for estimating plasma volume in ICU patients (Table 2), it provides only moderate accuracy when compared with the reference ^{125}I-labeled albumin technique [72]. Notably, the standard isotope method itself may overestimate plasma volume in septic patients, as the usual correction factor for transcapillary albumin

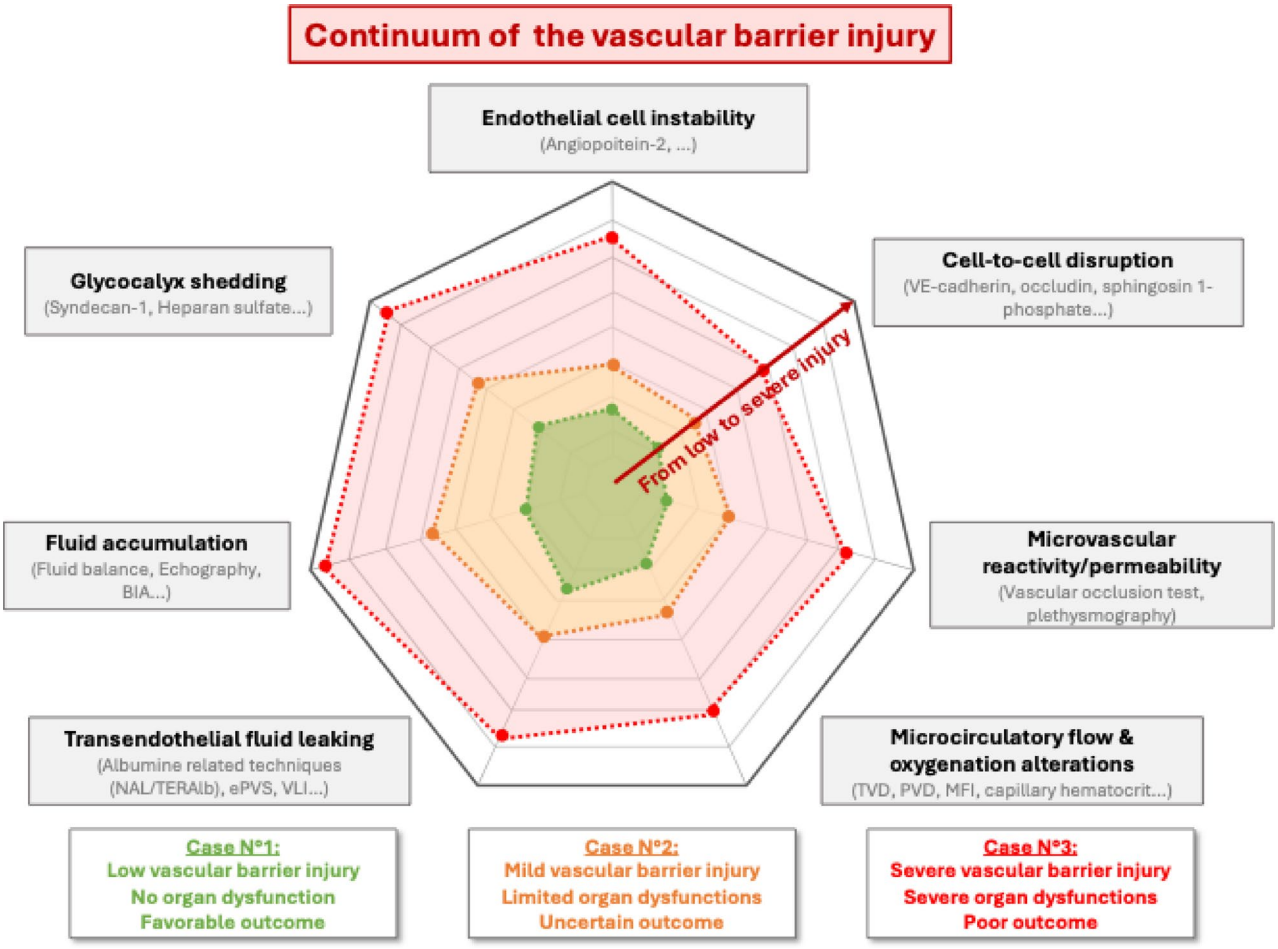


Fig. 3 Conceptual spectrum of vascular barrier injury and associated clinical consequences. This figure illustrates the conceptual continuum of vascular barrier injury across its different components and the resulting clinical implications. The examples of progression from low (Case N°1 / green radar plot) to severe vascular barrier injury (Case N°3 / red radar plot) corresponds to increasing endothelial dysfunction, fluid extravasation, and organ failure severity, translating into worse clinical outcomes. This framework is proposed as a hypothesis-generating conceptual tool and has not been prospectively validated. Abbreviations: BIA: Bioelectrical impedance analysis; NAL: Net Albumine Leakage; ePVS: estimated Plasma Volume Status, VLI: Vascular leak index, TVD: total vascular density, PVD: perfused vessel density, MFI: microvascular flow index, PBR: perfused boundary region

escape (2% in this study) is insufficient to account for the excessive leakage observed in sepsis.

More recently, a non-isotopic fluorescent technique has been developed to rapidly assess plasma volume and renal function using two labeled dextrans (150 kDa for PV and 5 kDa for glomerular filtration). However, this method has not yet been studied in critically ill patients [73].

Finally, the BVA-100 (Daxor, Oak Ridge, USA) is a semi-automated system that measures blood, plasma, and red cell volumes using radiolabeled albumin, providing a more accurate assessment of intravascular volume status [74]. Although early studies in sepsis have shown promising results, clinical evidence remains limited and further validation across diverse ICU populations is required [74].

Transcapillary escape rate of albumin (TER) These techniques enable calculation of the TER of albumin, which quantifies the proportion of albumin leaving the vascular compartment per unit of time. An elevated TER indicates increased vascular permeability and is derived from the rate of decline in plasma albumin concentration over time (Table 2). TER is approximately around 5% per hour under basal conditions in healthy individuals and increases in acute inflammatory states. In septic shock, values of approximately 6–7%/h have been reported, whereas higher TER values have been described after major surgical trauma, including cardiac and abdominal surgery, where additional inflammatory and hemodynamic factors may further accelerate albumin escape [75–77]. TER has several limitations, including variability across sampling protocols, sensitivity to plasma volume

changes, and assessment limited to intravascular albumin loss without accounting for lymphatic return. Additionally, the requirement for radiolabeled albumin restricts bedside feasibility, although newer semiautomated devices may address this issue.

Net albumin leakage (NAL) More recently, NAL has been proposed as a mass-balance approach integrating both albumin extravasation and lymphatic return. Derived from serial measurements of intravascular albumin mass (Table 2), NAL provides an indirect estimate of albumin accumulation within the interstitial compartment. In healthy individuals, NAL is expected to be close to zero, whereas positive values have been reported in conditions associated with increased vascular permeability, such as sepsis and major surgery [78–80].

NAL has the practical advantage of not requiring radiolabeled albumin and of explicitly accounting for lymphatic albumin return. It does not replace TER and should be interpreted as a complementary mass-balance index rather than a direct permeability coefficient. Its clinical application remains constrained by uncertainties in plasma volume estimation derived from blood volume equations validated in healthy individuals and the difficulty of defining baseline conditions in acute critical illness.

In summary, albumin-based techniques provide complementary information on intravascular volume and albumin distribution. While plasma volume measurements quantify the intravascular compartment, TER and NAL assess albumin movement across the vascular barrier over time. Although these methods remain indirect and compartment-dependent measures of vascular permeability, they are more closely linked to barrier function than plasma volume alone. Among them, NAL appears relatively simple to implement and may have potential for future clinical application.

Level 3 C: Microcirculatory and endothelial surface layer assessments

Microcirculatory analysis with handheld videomicroscopy Handheld video microscopy (HVM) using sidestream dark field and incident dark field imaging enables direct bedside visualization of the microcirculation, providing unique insights into tissue perfusion in critically ill patients [81]. Quantitative parameters such as total vessel density, perfused vessel density, and proportion of perfused vessels provide complementary structural and functional information about the capillary network, and can reveal microvascular flow heterogeneity and hemodynamic incoherence [82]. Beyond perfusion assessment, HVM can indirectly identify leukocyte–endothelial interactions and signs of fluid extravasation. Increased perivascular spacing and image blurring may reflect interstitial edema [83], a downstream consequence of capillary leak that increases oxygen diffusion distances and compresses small vessels, thereby reducing perfused vessel density [84]. These alterations have been reported to improve during fluid deresuscitation, in parallel with the resolution of tissue edema and recruitment of the microcirculation [85].

The perfused boundary region (PBR) is an intravital microscopy–derived index that estimates the depth of red blood cell penetration into the endothelial glycocalyx, with higher PBR values indicating greater glycocalyx thinning or degradation [86]. Increased PBR values have been described in various critical illness settings. However, recent data in sepsis suggest that PBR alterations are inconsistently associated with microcirculatory impairment as measured by classical consensus parameters, indicating that glycocalyx injury and microcirculatory flow abnormalities are related but not interchangeable phenomena [87]. PBR should therefore be interpreted as a marker of endothelial surface layer injury and one facet of endothelial dysfunction, rather than as a direct indicator of vascular permeability.

Overall, level 3 techniques remain complex and often compartment-specific. Most are insufficiently validated for routine bedside use or are confined to research settings and specialized centers. These limitations support a multimodal approach that combines complementary methods rather than relying on a single technique (Table 3).

Figure 2 provides an overview of the multimodal parameters that may contribute to the development of an integrated vascular permeability scoring system.

Vascular permeability in clinical practice: current challenges and further considerations

This narrative review highlights that no single bedside technique can comprehensively assess vascular permeability across different organs. Organ-specific differences in microvascular structure and interstitial compliance mean that similar increases in permeability may produce markedly different clinical consequences, particularly in the lung and kidney.

Although major advances have been made in understanding endothelial activation, glycocalyx injury, and capillary leak, translation into routine bedside monitoring and targeted therapies remains limited. This reflects the lack of an accepted reference standard for vascular permeability, the compartment-specific nature of current techniques, and the inconsistent relationship between mechanistic markers and clinical outcomes. In particular, glycocalyx degradation correlates only modestly with microcirculatory dysfunction or vascular leak,

and endothelial-targeted therapies have not consistently improved outcomes [89–92].

Current bedside tools measure only indirect consequences of barrier dysfunction—including endothelial injury, fluid redistribution, congestion, or tissue edema—rather than permeability itself. Biomarkers, laboratory-derived indices, and imaging each provide complementary but incomplete information and are influenced by systemic inflammation, organ function, and methodological variability [93–95]. In addition, the contribution of the lymphatic system remains largely unmeasured at the bedside [7, 13, 96].

Consequently, multimodal assessment is likely to provide greater clinical value than any single technique. Combining clinical examination, laboratory-derived indices, biomarkers, and bedside ultrasound may improve patient stratification and guide fluid stewardship while remaining integrated with conventional hemodynamic monitoring [18]. Rather than identifying a single "vascular permeability monitor", future work should focus on defining reproducible vascular barrier phenotypes that integrate endothelial injury, fluid redistribution, congestion, and microcirculatory dysfunction. Such a framework should also propose a pragmatic strategy for bedside monitoring, including an initial baseline assessment, reassessment of dynamic markers every 12–24 h, and additional evaluation following major therapeutic interventions or clinical deterioration. Defining clinically meaningful temporal changes that should trigger reassessment and outlining how these findings could inform therapeutic decisions—including fluid stewardship, deresuscitation, and, when available, endothelial-targeted therapies—will be essential for translating vascular permeability assessment into routine critical care practice.

From a pragmatic standpoint (Table 3), bedside assessment should be based on routine evaluation of edema and fluid balance, simple laboratory-derived indices (e.g. estimated plasma volume status or vascular leak index), and point-of-care lung and venous ultrasound, with reassessment after major therapeutic interventions or clinical deterioration. Grouping these tools into hierarchical levels highlights their complementarity: Level 1 methods provide accessible indicators of edema and congestion, whereas Level 2 techniques add biological and compartmental information that refines risk stratification. Such a multimodal strategy is more likely to improve fluid stewardship and deresuscitation than reliance on a single "vascular permeability monitor" and should complement, rather than replace, conventional hemodynamic assessment. Likewise, hemodynamic incoherence—persistent microcirculatory dysfunction despite adequate macrocirculation—represents a related but distinct monitoring target that may further inform resuscitation strategies [82].

Looking ahead, the greatest value of multimodal vascular permeability assessment may be in defining reproducible vascular barrier phenotypes rather than generating a single universal score (Fig. 33). By integrating markers of endothelial activation, glycocalyx injury, fluid redistribution, congestion, and microcirculatory dysfunction, patients could be classified along a continuum from mild endothelial activation without overt leak [90, 97, 98], to moderate injury with junctional disruption, edema, and microcirculatory dysfunction [98, 99], and finally to severe capillary leak syndrome with refractory edema and multiple organ dysfunction [18]. Similar phenotype-based approaches have successfully identified clinically meaningful sub phenotypes in ARDS and cardiogenic shock [100, 101]. Applying these strategies—potentially supported by machine learning—may enable earlier risk stratification and more individualized fluid, vasopressor, inotropic, and endothelial-targeted therapies. However, multimodal permeability scores still require external validation, and no study has yet demonstrated improved outcomes with permeability-guided resuscitation. Future research should therefore focus on validating vascular barrier phenotypes, developing practical real-time bedside tools, and testing phenotype-guided therapeutic strategies [99].

Conclusions

Vascular barrier permeability is a dynamic process central to critical illness, yet no bedside reference standard currently exists for its assessment. Available techniques provide complementary but indirect information and are best interpreted within a multimodal framework integrating clinical evaluation, imaging, laboratory-derived indices, and biomarkers. Future research should focus on standardizing measurement techniques, validating integrated assessment strategies, and leveraging artificial intelligence to define vascular barrier phenotypes and guide personalized therapy.

Abbreviations

ARDS	Acute respiratory distress syndrome
BALF	Bronchoalveolar lavage fluid
BIA	Bioelectrical impedance analysis
ECW	Extracellular water
ECW/TBW	Extracellular water-to-total body water ratio
ePVS	Estimated plasma volume status
EVLW	Extravascular lung water
HVM	Handheld video microscopy
ICU	Intensive care unit
NAL	Net albumin leakage
PBR	Perfused boundary region
PV	Plasma volume
PVPI	Pulmonary vascular permeability index
PVD	Perfused vessel density
PPV	Proportion of perfused vessels
TER	Transcapillary escape rate
TBW	Total body water
TPTD	Transpulmonary thermodilution
TVD	Total vessel density

TWI	Tissue water index
VLI	Vsascular leak index

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