



## REVIEW ARTICLE

### Novel Laboratory Biomarkers in Critically Ill Patients

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#### ABSTRACT

The crucial care placing desires early checks which permit clinicians to properly stratify patient hazard, to diagnose organ disorder early, and to set a focused remedy speedy. This raises the idea of biomarkers. An excellent biomarker check have to be secure, clean to perform, as non-invasive as viable, completed at the bedside or with a (quite) easy laboratory test, speedy, distinctly precise for the sickness, its subtypes and reasons, and touchy for as early detection as feasible. Biomarker checks were categorized clinically into: precursor, screening, indicative, stage, and predictive. Biomarker assessments can also contain measurements immediately on organic media or measurements which include brain imaging which do not contain direct sampling of organic media however measures modifications inside the composition or feature of the nervous system. The biomarkers mentioned in this article are biomarkers of cardiovascular illnesses, breathing illnesses, renal illnesses , as well as biomarkers of disorders of the nervous system , biomarkers of infection and biomarkers of gastrointestinal illnesses. A panel of biomarkers appears to be a probable answer for accomplishing a whole affected person assessment together with a good enough medical evaluation and tracking.

**Keywords:** Biomarkers; Critically ill; Cardiovascular; Respiratory; Renal.

#### INTRODUCTION

The crucial care placing desires early checks which permit clinicians to properly stratify patient hazard, to diagnose organ disorder early, and to set a focused remedy speedy. This raises the idea of biomarkers <sup>1</sup>.

As defined by the World Health Organization (WHO), a biomarker is “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome of disease” <sup>2</sup>.

The concept of the usage of biomarkers is to detect ailment and enhance remedy. Biomarkers, as changes within the materials of

tissues or body fluids, offer an effective technique to recognize the spectrum of illnesses with usage in as a minimum five fields: screening, analysis, prognostication, prediction of disorder recurrence, and healing tracking <sup>3</sup>.

There are numerous blessings of the use of biomarkers that include: goal evaluation, accuracy of measurement, dependability and they will help also in analyzing disorder mechanisms. Therefore, the translation of biomarkers can preserve to offer essential diagnostic and prognostic data <sup>4</sup>.

If expression of the marker varies periodically in reaction to intervention or other external influences, then the test can be useful

in adjusting the dosage and length of remedy. This could be very practical in the critical care daily usage <sup>5</sup>.

#### *Characteristics of an ideal biomarker*

New biomarker tests have to deal with the subsequent five “SAVED” questions for ideal medical translation. They consist of: is the biomarker probably to be: 1) Superior (will the check outperform contemporary requirements?); 2) Actionable (will the check alternate affected person control?); 3) Valuable (will the check enhance affected person consequences?); 4) Economical (will the implementation of the biomarker within the goal populace be price-saving or value-effective?); 5) clinically Deployable (is there a way for the biomarker and analytical technology to be carried out in a medical laboratory?) <sup>6</sup>. **Table 1** shows examples of biomarkers in different fields of medicine <sup>7</sup>.

This review article is written according to the guidelines of research ethical committee of Faculty of Medicine, Zagazig University.

### **CARDIOVASCULAR DISEASES**

Within the placing of myocardial ischemia and ensuing cell necrosis, Troponins might also boom as early as 2 hours after onset of acute myocardial infarction (MI), but might not be detected till up to six hours from the time of appearance, relying at the assay used. While, creatine kinase-MB (CK-MB) is generally arise within 4 to 6 hours after start of infarction. Because of this postpone in time to detection, a negative troponin or CK-MB drained on the time of illness doesn't exclude an acute MI and serial trying out is usually essential <sup>8</sup>.

Myoglobin is the first biomarker of myocardial damage to arise, allowing medical doctors to rule out the opportunity of myocardial infarction in a well timed style <sup>9</sup>. Heart-type fatty acid-binding protein (H-FABP) takes its section as a unique myocardial injury marker with analytic and predictive values within the control of acute coronary syndrome (ACS) affected person. The plasma level of H-FABP under normal situations is < 5µg/L <sup>10</sup>.

The function of assaying of serum β-type natriuretic peptide (BNP) or its N-terminal

prohormone, NT pro-BNP has been popular and integrated into suggestions for chronic cardiac failure. Extra these days, recommendations for acute cardiac failure have additionally advocated a unique test of BNP or NT pro-BNP in patients arriving with new suspected acute cardiac malfunction detected by the usage of echocardiography if BNP or NT pro-BNP quantities are increased. Serum BNP tests of < 100 pg/mL have negative predictive value (NPV) and of > 500 pg/mL have a 90% positive predictive value (PPV), for the diagnosis of congestive heart failure (CHF) <sup>11</sup>.

In venous thromboembolism (VTE), serum soluble P-selectin (sP-sel) has proven promise to afford a check high in specificity. Even though the D-dimer achieves high negative predictive values (NPVs) to rule out deep vein thrombosis (DVT), the high positive predictive values (PPVs) of sP-sel capable of rule in DVT <sup>12</sup>.

### **RESPIRATORY DISEASES**

Biomarkers offer an essential translational affiliation for comprehension of lung pathophysiology. Biomarker checking out has extended into the pathogenic function of epithelial cellular disorder, inflammation, and fibrosis in breathing illnesses. further, biomarker research may also assist us to discover the immune and molecular mechanisms of numerous healing techniques <sup>13</sup>.

Bronchial asthma is a not unusual breathing disorder characterised by means of reversible airway stumbling block, airway hyper responsiveness, and continual airway irritation, particularly with eosinophils. bronchial asthma is specifically as a result of sensitizing factors and outcomes from type 2 T helper cells (Th2) irritation characterized by interleukin (IL)-5, IL-13, mast cells, and eosinophils dominant inside the airway <sup>14</sup>.

Sputum eosinophils and increased fractional exhaled nitric oxide (FeNO) amount spot sick people with asthma very quick to respond to inhaled corticosteroid <sup>14</sup>. **Figure 1** shows changes in exhaled breath condensate mediators levels in severe asthma <sup>15</sup>.

In acute exacerbation of chronic obstructive pulmonary disease (COPD), Galectin-three (Gal-three), a b-galactoside-binding lectin, is considerably excessive. Serum Angiopoietin-2 and C-reactive protein ranges also are considerably increased at some stage in acute exacerbations of COPD <sup>16,17</sup>. Clinicians have to don't forget the occurrence of bronchial asthma in sufferers with COPD if the quantity of eosinophils within the peripheral blood is more than 200/ $\mu$ L <sup>14</sup>.

Reducing the period of pneumonia remedy can also successfully lessen selective stress using antimicrobial resistance without compromising sufferers' protection. Procalcitonin (PCT) steerage has been proven to be a value-effective adjunctive test <sup>2</sup>.

Novel fast microbiological assays, consisting of nucleic acid amplification, mass spectrometry, and fluorescence microscopy-based technology, multiplex polymerase chain reaction (M-PCR) of sputum samples in addition to exhaled breath biomarkers, such as volatile organic compounds (VOC) constitute destiny promising methods <sup>18</sup>.

Invasive pulmonary aspergillosis (IPA) is an severe sickness that calls for a excessive degree of medical suspicion for an early and correct analysis to enhance final results. Combining bronchoalveolar lavage (BAL) PCR with BAL galactomannan gives convincing diagnostic capability for IPA with eighty five% sensitivity and ninety seven% specificity <sup>19</sup>.

Carboxyhemoglobin (COHb) is an incredibly stable complex, and COHb release decreases oxyhemoglobin saturation, decreasing the discharge of O<sub>2</sub> to tissues. Nonsmokers not often come with COHb ranges above 1.5%, while people who smoke can come with COHb degrees as excessive as five%. degrees of COHb above 10-15% are steady with CO poisoning <sup>20</sup>.

MicroRNAs (miRNAs) be able to take part in crucial roles in inflammation and infection, that are not unusual picture of acute respiratory distress syndrome (ARDS). There are three hopeful miRNAs-miR-181a, miR-92a,

and miR424-which are linked to human ARDS <sup>21</sup>.

## RENAL DISEASES

Biomarkers for acute kidney injury (AKI) may be stratified into markers generally reflecting glomerular filtration (i.e. serum cystatin C), glomerular reliability (i.e. albuminuria and proteinuria), tubular strain (i.e. insulin-like growth factor binding protein7 ,tissue inhibitor metalloproteinase ), tubular harm (i.e. neutrophil gelatinase-related lipocalin, kidney damage molecule-1, N-acetyl- $\beta$ - D-glucosaminidase), liver fatty acid-binding protein (L-FABP), and intra-renal irritation (i.e IL-18) <sup>22</sup>. **Figure 2** shows biomarkers of AKI stratified according to site of insult <sup>22</sup>.

Medical control and healing intervention at in advance degree of diabetic nephropathy (DN) is of principal implication in avoiding reaching to end level renal ailment. Presently, the amount of albumin inside the urine is used as a widespread non-invasive check for the analysis of early DN. Continual microalbuminuria (among 30-300 mg/24 hr) or macroalbuminuria (ranges >300 mg/24 hr) is taken into consideration a marker and predictor of DN and its development to end stage renal disease (ESRD) <sup>23</sup>.

## DISORDERS OF THE NERVOUS SYSTEM

Glutathione S-Transferase- $\pi$  (GST- $\pi$ ) level is the most importantly increased biomarker within the blood of stroke sufferers with cut-off level approximately (65.2 ug/L). GST- $\pi$  can correctly expect the time of stroke onset in over 50% of early stroke sufferers and this check ought to, consequently, supplement cutting-edge suggestions for tissue plasminogen activator (tPA) management and probably boom the quantity of sufferers gaining access to thrombolytic remedy <sup>24</sup>.

The Triage Stroke Panel, a multimarker check, detects serum B-type natriuretic peptide (BNP), D-dimer , matrix metalloproteinase-9 (MMP-9), and S100B protein and right away generates a multimarker index of those values, which has been certified for diagnostic functions as it'd boom the validity of the

medical analysis to distinguish among stroke imitating illnesses and actual ischemic strokes<sup>25</sup>.

Cerebrospinal fluid (CSF) lactate enables in differentiating bacterial from viral meningitis. Whilst at a cut-off level of 3 mmol/L, CSF lactate has excessive diagnostic accuracy for bacterial meningitis, imply ranges in viral meningitis continue to be basically beneath 2 mmol/L<sup>26</sup>.

### SEPSIS

Performance of antibiotic stewardship helps to control needless antibiotic prescribing in addition to make certain the performance of remedy. a really perfect marker need to help early analysis and abilities to monitor the sickness and facilitate the healing interventions and choices. An set of rules primarily based on serial assays of PCT can lessen the antibiotic administration in septic sufferers. according to amount of serum PCT, healing selections in sufferers had been taken (**Figure 3**)<sup>27</sup>.

Soluble CD14 subtype (sCD14-ST) additionally referred to as presepsin elevates considerably all through inflammation and appears to be usable in differentiating among bacterial and nonbacterial infections. Presepsin

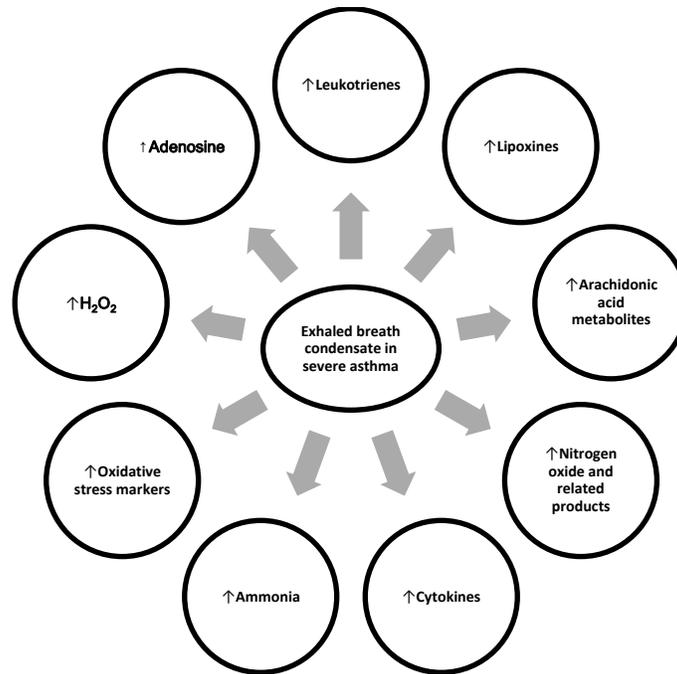
is generally found in very low concentrations in the serum of healthful people. In reaction to bacterial infections, its level elevates in 2 hours, consistent with the severity of the disorder. Plasma diagnostic cut-off ranges for sepsis are among 400–600 pg/ml<sup>28</sup>.

Testican-1 is a surprisingly multidomain proteoglycan that is utmost prominently expressed inside the thalamus of the brain, and is upregulated in activated astroglial cells of the brain. In sufferers admitted to the intensive care unit (ICU) with sepsis, circulating blood ranges of Testican-1 have been considerably excessive (range 20.44–63.37 ng/ml) and that they prominent with the rigorousness of sepsis<sup>29</sup>.

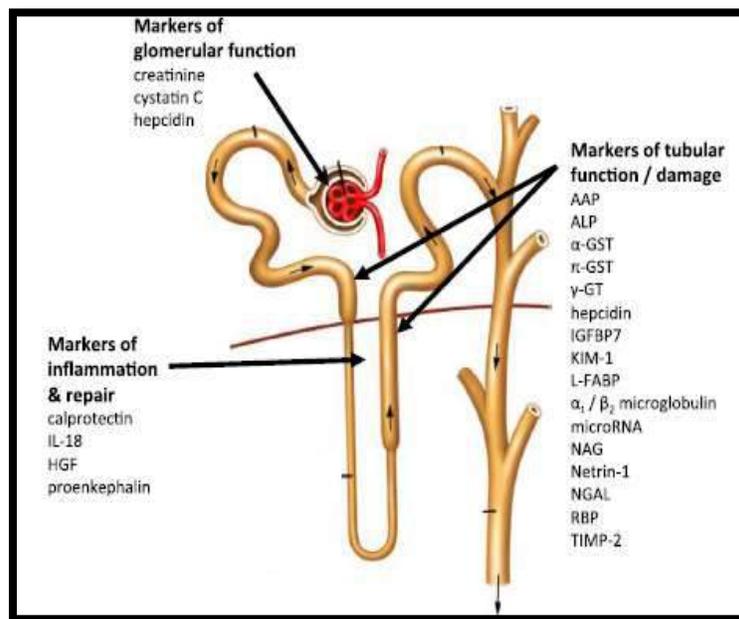
Coenzyme Q10 (CoQ10) is a molecule produced inside the mitochondrial internal membrane that exists each in oxidized form (ubiquinone) and reduced form (ubiquinol). figuring out low CoQ10 ranges in sepsis is great because the compound is crucial to mitochondrial characteristic and can play an critical function within the pathophysiology of sepsis. It opens the opportunity for ability healing intervention as CoQ10 may be administered exogenously<sup>30</sup>.

**Table (1): Examples of biomarkers currently used in different fields of medicine<sup>7</sup>**

Field of medicine	Disease	Screening to identify at-risk patients (primary prevention)	Diagnostic for existent disease states (secondary prevention)	Prognostic for treatment and outcomes (tertiary prevention)
Cardiovascular	Cardiovascular disease	Serum low-density lipoprotein cholesterol	Coronary artery computed tomography screening	Echocardiographic left ventricular ejection fraction as a prognosticator for sudden cardiac death
Endocrinology	Diabetes mellitus	Fasting blood glucose	Microalbuminuria screen for diabetic nephropathy	Hemoglobin A1C % and long-term glucose control
Gastroenterology	Colon cancer	–	Colonoscopy	Carcinoembryonic antigen for postsurgical colon cancer recurrence
Rheumatology	Systemic lupus erythematosus	–	Anti-smith antibody specific for detecting lupus	Anti-dsDNA for diagnosis of lupus nephritis
Oncology	Breast cancer	BRCA-1 gene BRCA-2 gene	Mammography	Tumor estrogen receptor, progesterone receptor and HER2-neu receptor status for decisions about tamoxifen therapy



**Figure 1.** Changes in exhaled breath condensate mediators values in severe asthma <sup>15</sup>



**Figure 2.** Biomarkers of AKI <sup>22</sup>. α-GST α glutathione S-transferase, AAP alanine aminopeptidase, ALP alkaline phosphatase, γ-GT γ-glutamyltranspeptidase, π GST π glutathione S-transferase, HGF hepatocyte growth factor, IGFBP-7 insulin like growth factor binding protein 7, IL-18 interleukin 18, KIM-1 kidney injury molecule-1, L-FAB liver fatty acid-binding protein, NAG N-acetyl-β-D-glucosaminidase, NGAL neutrophil gelatinase-associated lipocalin, RBP retinol binding protein, TIMP2 tissue inhibitor metalloproteinase 2.

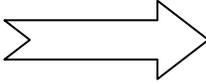
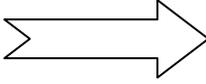
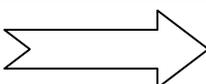
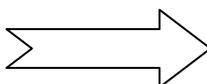
>0.5ng/ml		<b>Antibiotic strongly encouraged</b>
0.25-0.5ng/ml		<b>Antibiotics encouraged</b>
0.1-0.25ng/ml		<b>Antibiotics discouraged</b>
<0.1ng/ml		<b>Antibiotics strongly discouraged</b>

Figure 3. Procalcitonin algorithm for antibiotic therapy <sup>27</sup>

**GASTROINTESTINAL DISEASES**

Serum alanine and aspartate aminotransferases (ALT/AST) were the gold popular for detection and quantification of liver damage, however have rather lengthy half-lives (T ½) (about 17 and 47 h, respectively) and for that reason do now not mirror on the spot modifications in liver damage or healing. Novel immunoassay α-glutathione S-transferase (α-GST) measures this cytosolic liver enzyme with a anticipated T½ of 60–90 min would possibly allow in advance detection of enhancing or worsening liver damage than traditional enzyme checking out <sup>31</sup>.

Urinary trypsinogen activation peptide (uTAP) has the capability to behave as a classification marker on admission for evaluating rigorousness of acute pancreatitis (cut-off level 35 nmol/L) <sup>32</sup>.

Serum elastase is a protease found in pancreatic discharge reaches the colon without being cleaved and isn't tormented by intestinal transit instances or pancreatic enzyme substitute remedy. Serum Elastase e1 range is used for the analysis of acute or chronic pancreatitis, pancreatic insufficiency with proper diagnostic accuracy. Fecal elastase plays higher in moderate to extreme pancreatic Insufficiency <sup>33</sup>.

In severely ill sufferers, the gut is a susceptible organ, and gastrointestinal (GI) disorder is not unusual. Amongst critically unwell sufferers, people with GI disorder have more mortality rates than the ones without GI

disorder. It's far consequently important to screen the reputation of the GI tract in seriously unwell sufferers. Markers like serum intestinal fatty acid binding protein (i-FABP), lipopolysaccharide (LPS), as well as D-lactate (D-la.), had been proposed as feasible markers for intestinal barrier feature and the detection of acute gastrointestinal injury (AGI). Increased serum ranges of i-FABP, LPS and D-la can mirror GI barrier disorder and acute GIT harm. the subsequent values are references of ordinary serum ranges of those biomarkers (i-FABP (24.54–34.87pg/mL),LPS(1.17–3.45pg/mL), D-l. a. (3.23–10.37µmol/L) <sup>34</sup>.

**CONCLUSION**

Each organ disorder is a part of a complicated community of relationships with different organs and, consequently, using a one biomarker has a restricted benefit within the whole affected person assessment. A panel of biomarkers appears to be a probable answer for attaining a entire affected person evaluation collectively with a good enough medical assessment and tracking.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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None declared

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