Prognostic Biomarkers in Patients with Acute Myocardial Infarction

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Despite all the important advances in its diagnosis and treatment, acute myocardial infarction (AMI) is still one of the most prominent causes of morbidity and mortality worldwide. Early identification of patients at high risk of poor outcomes through the measurement of various biomarker concentrations might contribute to more accurate risk stratification and help to guide more individualized therapeutic strategies, thus improving prognoses.

biomarkers   myocardial infarction   prognosis

1. Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide, with an estimated 17.9 million deaths annually [1]. Despite all of the important advancements in diagnosis and treatment, more than four out of five cardiovascular deaths are caused by acute myocardial infarction (AMI) and stroke [1][2]. Myocardial infarction is most often caused by a rupture or erosion of an atherosclerotic plaque involving acute atherothrombotic occlusion of an epicardial coronary artery [1]. The clinical definition of myocardial infarction relies on the presence of acute myocardial injury detected from abnormal cardiac biomarkers, especially cardiac troponin (cTn), in the identification of evidence for acute myocardial ischemia [3]. Myocardial infarction can be classified as ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), which determines the treatment strategy that is needed [1][3]. Patients with STEMI often have a higher incidence of transmural ischemia, a larger area of infraction and worse short-term prognosis in comparison with patients that present with NSTEMI. Reserved prognoses for patients with acute myocardial infarction involve a large area of infarction, development of left ventricular dysfunction and adverse remodeling [1]. Early identification of patients at high risk of poor outcomes through the measurement of various biomarker concentrations soon after the onset of MI might contribute to more accurate risk stratification in these patients. By assessing the risk for patients with acute myocardial infarction, therapeutic strategies can be tailored to each patient's needs, thereby improving patients' prognoses [4][5][6][7][8].

An ideal biomarker should have a high sensitivity and specificity, as well as several clinical and assay-related characteristics, such as a good cost-effectiveness ratio, short processing time and high precision. These characteristics ensure a straightforward assay process to guide therapy and predict the prognosis of patients. Currently, there is no single ideal biomarker that can improve risk prediction for patients with AMI; it is a considerable challenge for clinicians to discover an ideal biomarker. Thus, in order to identify novel predictive biomarkers, researchers have used proteomic technologies. Proteomics have been used to highlight the significant

alterations in the cardiac proteome following an MI. A proteomic study of unstable plaques also revealed new evidence about the pathologic processes of plaque rupture [9]. This complex process involves changes at the cellular and molecular levels that impact ventricular size, shape and function after an AMI [10]. A study conducted by Shavadia et al. evaluated the associations between 24 h relative changes in the concentrations of 91 novel biomarkers and composite outcomes in 139 STEMI patients (72 cases, 67 controls) treated with primary percutaneous coronary intervention. The authors observed that the variations in the expression of 14 biomarkers linked with myocardial fibrosis and remodeling, inflammation, thrombosis and angiogenesis and cholesterol metabolism were substantially correlated with the outcomes within 90 days. Their results suggest the need to include synergistic multi-biomarker strategies for risk stratification in patients with AMI [11]. The use of multi-biomarker proteomics may also be combined with machine learning, as was undertaken for general cardiovascular risk by Williams et al. [12]. Machine-learning techniques can be used to design a protein model in order to determine the probability of outcomes of post-myocardial infarction.

Although there is no ideal biomarker that can provide prognostic information for risk assessment of patients with AMI, the results from recent years are promising [8][13][14]. For instance, several novel biomarkers have been identified that may bring additional value for AMI prognosis when included in multi-biomarker strategies. There is no generally accepted classification for these prognostic biomarkers; many of them fall into more than one category. To facilitate a better understanding, they can be distributed according to their pathogenesis as follows: biomarkers of inflammation, biomarkers of myocardial necrosis, neurohormonal activation biomarkers, cardiac remodeling biomarkers and vasoactive biomarkers (**Figure 1**).
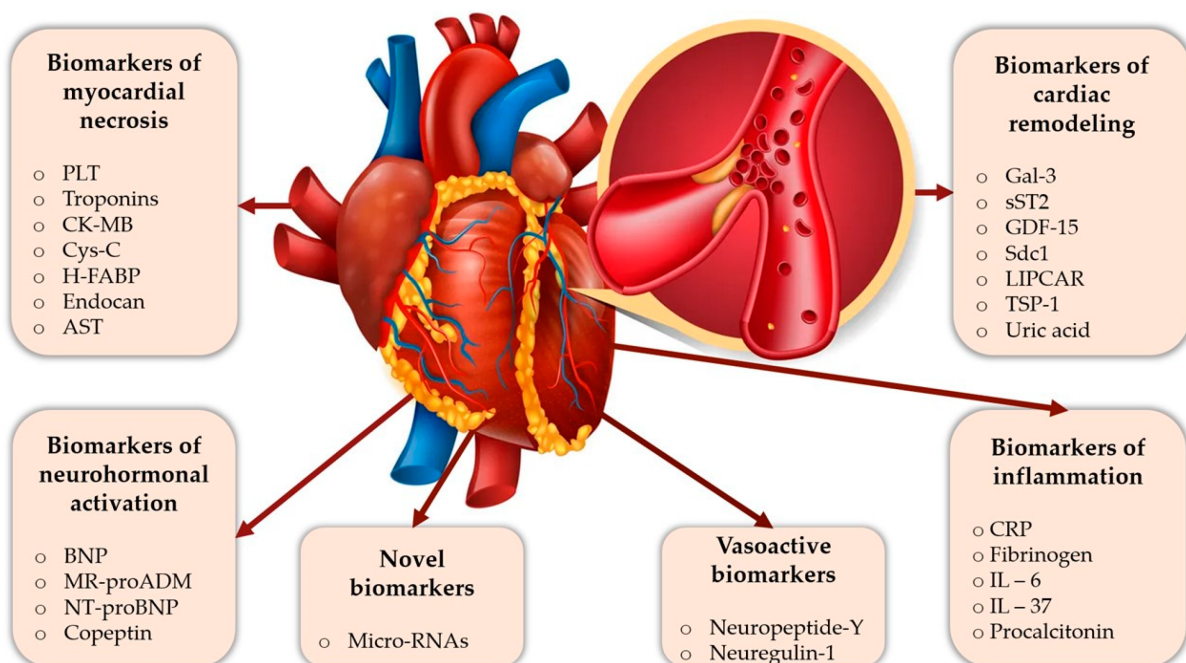

Figure 1. Prognostic biomarkers in patients with acute myocardial infarction. AST, aspartate transaminase; BNP, brain natriuretic peptide; CK-MB, creatine kinase-MB; cysC, cystatin C; CRP, C-reactive protein; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; H-FABP, heart-type fatty acid binding protein; IL-6, interleukin-6; IL-37, interleukin-37; LIPCAR, a long noncoding ribonucleic acid; MicroRNAs, microribonucleic acids; MR-proADM, mid-

regional proadrenomedullin; NT-proBNP, N terminal pro-brain natriuretic peptide; PLT, platelet; Sdc-1, syndecan-1; sST2, soluble suppression of tumorigenicity-2; TSP-1, thrombospondin-1.

2. Biomarkers of Inflammation

2.1. C-Reactive Protein

C-reactive protein (CRP) has become one of the most studied biomarkers of inflammation due to the fact that atherothrombosis represents a large majority of acute myocardial infarctions, and CRP is strongly associated with this type of pathogenesis. As an acute phase protein, CRP levels are elevated in inflammatory or infectious processes due to the liver's response to high concentrations of plasma cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Increased levels of CRP have been reported as an independent predictive biomarker for cardiac or noncardiac death and even for recurrent nonfatal events, with detection of CRP at 4–6 h after the occurrence of AMI and a peak level of CRP after about 50 h [4][5]. Furthermore, CRP is directly involved in the generation of endothelial dysfunction in the process of atherosclerosis. Therefore, through the inhibition of the eNOS at the endothelial level, a decrease in nitric oxide synthesis results, which further leads to inhibition of angiogenesis, vasoconstriction and inflammation. In addition, CRP is part of the process of microvascular thrombus formation and, thus, microvascular obstruction through the development of leucocyte adhesion and platelet aggregation in the ischemic endothelium [6]. Usually, there is a strong inflammatory response after an AMI. This is defined by the following: secretion of cytokines and chemokine; expression of adhesion molecules on endothelial cells; activation of the complement cascade with secondary release of proinflammatory cytokines, which ultimately trigger myofibroblasts; and expression of matrix proteins, which play a protective role in the infarcted area [7]. CRP is an important biomarker in this case simply because it reflects the prolongation of the temporal and spatial inflammatory process. Hence, the higher the CRP value is, the larger the inflammatory response. To some degree, it may even reflect the size of the myocardial infarction area, which is strongly related to post-infarct left ventricular (LV) dysfunction [8][13]. Extremely elevated levels of CRP ≥ 20 mg/dL have been associated with severe inflammatory processes; as a result, CRP is a predictor value for ventricular aneurysm and subacute cardiac rupture [14]. Ming et al. [4] found that serum concentrations greater than 8.95 mg/L at admission are associated with cardiovascular, cardiac and long-term all-cause mortality after an AMI, regardless of the presence of diabetes mellitus. In a meta-analysis including seven studies (six retrospective studies and one cohort study), the elevated CRP group presented predictive values for greater risk of in-hospital and long-term mortality, major acute cardiovascular events (MACEs) and recurrent AMI, but without acute or subacute in-stent restenosis [15]. It has been postulated that every 1 mg/L in the CRP value correlates with a 12% increase in the risk of MACEs [13]. With the advancement of technology, much more sensitive determinations have been discovered, such as highly sensitive CRP (hs-CRP), which can detect much lower levels of CRP, around 0.5–1 mg/L compared to 5–20 mg/L in the case of classical moderately sensitive immunoassays for CRP [5]. There is scientific evidence that patients with hs-CRP values > 2 mg/L measured 30 days post-AMI (indicating persistent inflammatory response after the acute phase) have a two-fold increase in the risk of a new heart failure (HF) or of the worsening of an existing heart failure over the following 2 years [13][16]. At the same time, hs-CRP is not limited to predicting HF; it can also predict

recurrent ischemic events and cardiovascular death. In a study conducted by Maarten et al. [16], it was found that only the peak CRP determined in the acute phase is statistically relevant for predicting left ventricular dysfunction (LVD) at follow-up. Christian et al. [17] demonstrated that peak CRP levels are a strong predictor for all-cause and cardiovascular mortality at one-year follow-up after ST-elevation myocardial infarction (STEMI). Moreover, CRP concentrations greater than 10 mg/L within 12 h after hospitalization predicted a 6% increase in the risk of poor evolution. This can imply left ventricular systolic dysfunction (LVSD) in short- and long-term follow-up, therefore suggesting an opposed correlation between in-admission CRP determination and left ventricle ejection fraction (LVEF) in multi-year follow-ups [13]. Iwona et al. [18] studied the prognostic value of CRP in patients with STEMI followed by percutaneous coronary intervention (PCI) and guideline-based treatment. Remarkably, there was a relation between persistently increased levels of CRP at admission and one month after discharge and an elevated risk for HF hospitalization and mortality in six years of follow-up. A single-center observational study [19] assessed the association between increased CRP and the risk for acute kidney injury (AKI) in STEMI patients treated with PCI; their study demonstrated that CRP is an independent marker for AKI in this category but with limitations in determining the adequate moment for measurement of its value during the 24 h after admission. Furthermore, Fu et al. [20] recently suggested that, in post-AMI patients treated according to guidelines, an increased hs-CRP ≥ 2 mg/L is related to later risk of AKI and progression of chronic kidney disease (CKD), regardless of baseline kidney function. In a prospective study, Ozgur et al. [21] demonstrated that the CRP to albumin ratio may also present potential usefulness as a predictor for poor clinical evolution in short-term follow-up of patients with STEMI, regardless of the number of vessels affected, but without precision in the assessment of the localization and width of the ischemic area.

2.2. Fibrinogen

Fibrinogen (FIB) was one of the first clotting factors to be identified. It was first studied in the 19th century and represents an acute phase protein produced in the liver. Its effects are multiple, including on platelet aggregation, endothelial lesions, plasma viscosity and the fibrinolysis system, and it is therefore directly implicated in the formation of thrombi [22][23]. Through interactions with inflammatory cytokines, FIB has a significant role in the inflammatory response, impacting the onset and progression of cardiovascular disease. Furthermore, coronary artery restenosis can be provoked secondarily to FIB degradation products, which promotes smooth muscle cell proliferation [23]. Ang et al. [24] suggested that, in patients with acute coronary syndrome (ACS) after PCI, a higher baseline fibrinogen value (≥280 mg/dL) is correlated with an increased risk of MACEs within two years. These are defined as rehospitalization, revascularization, stent thrombosis, stroke or transient ischemic attack (TIA) and all-cause mortality. Earlier studies suggested cut-off values greater than 350 mg/dL for the same outcomes [25]. In addition, in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) treated with PCI, fibrinogen was an independent predictor of non-fatal infarction or death and was indistinguishable from the GRACE system score in anticipating such outcomes [23]. Some research has found that the fibrinogen to albumin ratio (FAR) has a more relevant link to clinical events than albumin and fibrinogen alone, being an independent predictor of MACEs in patients treated with PCI for ACS. The presence of albumin is not surprising, as it is a serum protein with important roles not only in the regulation of osmotic pressure in extracellular fluid but also in platelet aggregation through its increase of the production of prostaglandin D2. A low concentration of albumin may lead to endothelial dysfunction

and was found to be an independent risk predictor for all-cause mortality at 40 months follow-up in patients with STEMI [25]. Being a feasible marker, as well as a cheap one, FAR could be considered a potential alternative tool to amplify the prognostic sensitivity value in patients with STEMI [26]. In addition, Liu et al. [27] studied the relationship between FAR and the SYNTAX score, demonstrating that there is a linear connection in this case, as well as benefits such as simplicity, efficiency and exhaustiveness. Furthermore, it has been suggested that high levels of pre-procedural FIB are an independent risk marker for contrast-induced kidney injury after catheterization in patients with ACS [23][28].

2.3. Interleukin-6

Interleukin-6 (IL-6) is one of the most important cytokines. It is produced by T-cells and macrophages in response to a trauma or to an infection and involves hepatic CRP liberation in the second stage of the process [29]. It may also be considered as a pivot in inflammatory signaling during the atherosclerosis process, and it has a negative impact on myocardial architecture and function, leading to cardiac remodeling, and associations with the severity of the coronary atherosclerosis considered in relation to the size of the ischemic area or the presence of HF [30][31]. Usually, higher levels of IL-6 are related to white race, female sex, impaired renal function (eGFR < 60 mL/min/1.73 m^2), current smoking and severe coronary lesions [32]. Ridker et al. demonstrated that admission levels of IL-6 were predictive for future significant MACEs, such as non-fatal myocardial infarction, non-fatal stroke, cardiovascular death and MACE plus hospitalization for unstable angina requiring urgent revascularization [33][34]. In addition, compared to the lowest IL-6 levels, the highest levels were linked to a more than twofold greater risk for HF hospitalization and correlated with negative outcomes independently of recognized risk predictors and biomarkers (hs-CRP, highly sensitive troponin I (hs-TnI) and brain natriuretic peptide (BNP)). By stimulating the production of the matrix metalloproteinase (a protein family implicated in collagen production), IL-6 can increase fibrosis and cardiac remodeling, which are important aspects in the generation of HF over time [32].

2.4. Interleukin-37

Interleukin-37 (IL-37) is an interleukin-1 (IL-1) family cytokine found in low levels in multiple locations, such as the brain, heart, colon, prostate and tonsils, and even in epithelial cells, keratinocytes, plasma cells, monocytes and macrophages [34]. Being an immunosuppressive factor, IL-37 plays a central role in both adaptive and innate immunity [35]. Kun et al. performed a case-control study in patients with ACS undergoing primary PCI. Their study revealed that the baseline levels of IL-37 were, surprisingly, higher in the ACS patients (p < 0.05) compared to those with stable or without angina, especially in those with an electrically ischemic modification (p < 0.05), its levels being steadily elevated in relation to the degree of coronary artery disease (CAD) [36]. In addition, the same study [36] illustrated that reduced LVEF and raised N terminal pro-brain natriuretic peptide (NT-proBNP) levels correlated with increased levels of IL-37 before PCI, thereby independently anticipating in-hospital MACEs, acute HF, cardiac death, non-fatal myocardial infarction and target lesion revascularization (TLR). Although the anti-inflammatory mechanism of IL-37 in patients in ACS is yet to be definitively elucidated, Kun et al. proposed its role in the suppression of an acute and uncontrollable inflammatory process to be a feedback loop [36]. It has been anteriorly described that the expression of IL-37 is involved in the pathogenesis of atherosclerosis and that this

biomarker has an inflammatory effect by reducing the expression of other inflammatory cytokines, such as interleukin-18 (IL-18) and TNF-α. Therefore, a stronger inflammation process may be associated with greater IL-37 levels. Moreover, higher levels of IL-37 expression on admission were positively associated with a greater mortality risk than lower levels [37].

2.5. Procalcitonin

Procalcitonin (PCT) is an inactive precursor of calcitonin implicated in calcium homeostasis. Strong bacterial infections, major surgery and burns, various traumas and cardiogenic shock are some of the situations where serum PCT levels are greatly increased [22]. In recent years, PCT has received a lot of attention. It has been seen as a marker of the inflammatory response generated by AMIs. Dai et al., in a study that assessed the relation between myocardial infarction risk and plasma PCT levels, showed that an elevated concentration of PCT (immediate and average levels) was related to an increased risk of significant adverse cardiac events [38]. In contrast, other research has demonstrated the opposite effect. In a series of studies, PCT was recognized more as an infection predictor marker than a MACE post-ischemic factor. In a prospective trial, Barkey et al. concluded that PCT is more effective for ruling out infection, being a better biomarker than elevated CRP serum, white blood cell count and fever with a cut-off value of ≤0.09 ng/mL [39]. Reindl et al. measured the serum levels of PCT in patients with STEMI undergoing primary PCI within 24 h after pain onset (24 h and 48 h after the procedure) and compared them with cardiac magnetic resonance (CMR) markers for cardiac injury. The study found that serum PCT levels were not correlated with LV remodeling and negative clinical outcomes after an AMI [40]. Pavasini et al. [41] confirmed the role of PCT in predicting bacterial infection in patients hospitalized for ACS and cardiogenic shock ($p < 0.001$), even if its levels were greater in this group of patients despite not being associated with long-term outcomes or in-hospital mortality [42]. In addition, Hashemipour et al. assessed the association between the Gensini score as a measure of the severity and extent of CAD and PCT levels as a marker of inflammation in patients. They concluded that there was no statistical significance for the relationship between the two [43].

3. Biomarkers of Neurohormonal Activation

3.1. B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a hormone produced as a consequence of ventricular dysfunction. Being secreted by cardiac cells, its roles include inhibition of the renin-angiotensin-aldosterone system, natriuresis and vasodilatation [44]. Recently, there has been interest in the deeper field of view; truncated molecular forms of BNP, such as BNP 5-32, BNP 4-32 and BNP 3-32, have appeared. Zubair et al. studied these types of molecules in 1078 patients with AMI. The focus was on the predictive capabilities of these molecules. The conclusion was that all of them were independently capable of predicting death, reinfarction, rehospitalization and MACEs, not only at 6 months, but also at 1 and 2 years after the main event. Therefore, they are associated with poor prognosis. In addition, BNP 5-32 was capable of improving upon the GRACE risk score for death at 6 months in combination with NT-proBNP. It could be considered a secondary risk stratification in these patients, particularly in low-risk form [45]. Carvalho et al. postulated that every modification that appears in BNP levels further leads to enhanced risk

prediction, even in patients that do not experience associated HF in the course of an AMI. Furthermore, two measurements of BNP values, at days 1 and 5 after the event, were found to add a supplementary predictive aspect to the GRACE score system in comparison with using only a single measurement upon admission. Moreover, the same study reflected on the possible use of this biomarker for left ventricular degradation function at 30 days after STEMI when detected at significant levels. At the same time, it has been correlated with congestive HF, recurrent MI and mortality, regardless of short- or long-term follow-up [46]. Wolsk et al. demonstrated that, in patients with recent ACS associated with type 2 diabetes mellitus (which is known to interfere with values of BNP, regardless of the presence of a cardiovascular comorbidity), BNP along with NT-proBNP were great predictors not only for heart failure ($p < 0.001$) and death ($p < 0.001$) but also for stroke and myocardial infarction [47]. Moreover, in a study that included 180 patients with first-time AMI and primary PCI and follow-up at one year, Yan-Peng et al. examined the correlation between BNP and ST 2, IL-33 and MACEs. They observed that there was an important elevation in patients presenting with AMI with MACEs in comparison to those who did not present any MACEs. Moreover, there was a more diminished one-year survival rate. Another study observed a positive relationship between BNP, ST 2 and IL-33 and Gensini score; therefore, these markers were found to be assets for prediction of MACEs in a patient that had an AMI and underwent primary PCI [48]. Recently, Jun-Won et al. demonstrated that, in patients with AMI, in a prospective single-center PCI registry in which there was a measurement of BNP levels at admission and at follow-up of 2 months, short-term follow-up level after discharge was a stronger prognostic biomarker for MACEs and all-cause mortality [49]. Kazuhiro et al. described a particular situation: in patients with AMI and impaired glucose tolerance (IGT), high serum levels of BNP could predict the worsening of HF, the appearance of coronary stenosis and recurrent MI [50]. Furthermore, a fourfold increase in the risk of experiencing adverse cardiovascular outcomes at 10 months was observed in subjects with high BNP levels (>80 pg/mL) when compared with subjects who had consistently lower levels [51].

3.2. Mid-regional Proadrenomedullin (MR-proADM)

Adrenomedullin (ADM), initially isolated from a pheochromocytoma tissue, is a ubiquitous peptide present in physiological conditions in vascular, renal, adipose, pulmonary and cardiac tissue. Increased plasma levels in patients with different diseases, such as congestive heart failure, hypertension, diabetes mellitus and myocardial infarction, were stimulated by volume overload [52][53]. Given its role in vasodilatation, natriuresis through inhibition of the aldosterone secretion, endothelial function and cardiac contractility, it is strongly correlated with the normal functioning of the cardiovascular system and is a good predictor of the risk for cardiac and non-cardiac death in heart failure patients [52][54]. Nonetheless, because of ADM's short half-life in the bloodstream, its measurement is difficult. However, the assessment of mid-regional proadrenomedullin (MR-proADM), a precursor molecule of ADM with greater stability, is feasible [52][53]. A recent prospective study that evaluated the relationship between MR-proADM and the left ventricular function after an MI concluded that this biomarker is an independent positive predictor of adverse remodeling, one of the main causes of heart failure, and a negative marker of reverse remodeling [55]. The Danish Study of Optimal Acute Treatment of Patients With STEMI (DANAMI-3) found that high MR-proADM levels (≥0.79 nmol/L) prior to PCI in patients with STEMI were strongly associated with an elevated risk of short- and long-term all-cause or cardiovascular mortality and hospital admission for heart failure [56].

Furthermore, increased levels of mid-regional proadrenomedullin, measured within 24 h in patients with ACS and cardiogenic shock, were found to be a predictor of in-hospital mortality (p = 0.024) [54].

3.3. N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP)

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a prohormone released by cardiac cells in response to either myocardial stretching or an AMI. Despite the properties of BNP, NT-proBNP is associated with stability and a longer half-life time [57]. Moreover, natriuretic peptides have been proposed as a useful tool to indicate the degree of LV dysfunction in ischemic heart disease, arrythmias and cardiomyopathies, thus suggesting a need for a more intense approach to lower ventricular wall stress [58]. In a multivariable COX model study applied to an NSTEMI cohort, Gong et al. found NT-proBNP to be an independent risk factor for composite MACEs at 12 months after discharge, including all-cause mortality, hospital admission for unstable angina or heart failure, non-fatal recurrent myocardial infarction and target lesion revascularization (HR: 2.19, p = 0.0002). Furthermore, in patients older than 60 years old who were associated with an LVEF lower than 40%, this turned out to have a stronger prognostic value. Additionally, a positive correlation was found between NT-proBNP and the GRACE score (r = 0.58, p < 0,0001) [57]. In a retrospective study that included more than 200 patients with STEMI undergoing PCI, Zhao et al. studied the relationship between the presence of fragmented QRS (fQRS) in electrocardiograms in more than three leads or anterior leads and NT-proBNP as a prognostic marker of decreased regional ventricular systolic function [59]. The secondary analysis biomarker sub-study in the Platelet Inhibition in Patient Outcomes (PLATO) study found a substantial correlation between NT-proBNP levels and all-cause death after an ACS (HR: 2.96), as well as death secondary to HF (HR: 8.20), arrythmia (HR: 3.89) and sudden cardiac death. Therefore, it can be considered a predictive biomarker for all-cause and cause-specific mortality [60]. According to Tiller et al., in patients with STEMI undergoing primary PCI, the levels of NT-proBNP at admission were increased in those with an infarct size greater than 19% of the LV myocardium as evaluated by cardiac magnetic resonance imaging in comparison with those with a smaller affected area (140 ng/L vs. 86 ng/L, p = 0.008), an early assessment of the amount of the cardiac damage being an essential instrument for post-STEMI risk stratification [61]. Celebi et al. [62] showed that a single determination of NT-proBNP levels being greater than 400 pg/dL within 12 h offers a predictive value for LV aneurysm (LVA) development. A study by Zhang and Guo [63] revealed that high peak NT-proBNP levels were independently correlated with early onset LVA (OR: 1.08, p = 0.031), along with female sex, QS waves on electrocardiogram (ECG) and wall motion dysfunction.

3.4. Copeptin

Copeptin is one of the biomarkers used in cardiovascular disease, as the C-terminal part of the pro-arginine vasopressin is secreted in equimolar quantities with it, and it also presents great stability in biological samples [64]. In the case of AMI, copeptin is known to show increased values immediately, after which the values decrease until the third to fifth days after the event, when it reaches a plateau phase. It has been shown that it may be a good prognostic factor for STEMI, as well as for HF or ischemic stroke [65]. Lattuca et al. demonstrated, in an unselected cohort of 401 STEMI patients, that values of copeptin determined at admission presented an independent and feasible prognostic marker for one-year mortality (p = 0.022), being even better than the peak cardiac troponin I

levels studied under the same conditions. Copeptin could encourage more aggressive treatment [66]. Furthermore, Ahmed et al. also proved the greater value of copeptin compared to troponin I for NSTEMI patients and its prognostic value for MACEs (cardiac death, re-infarction, re-hospitalization for ischemic events, HF, stroke and TLR) and coronary revascularization within one year of follow-up ($p < 0.001$ for each) [67]. In a study conducted by Marta et al. [64] that included 100 patients with AMI undergoing primary PCI, increased copeptin levels on the fourth/fifth day, but not on admission, were associated with MACEs (re-infarction, unscheduled coronary revascularization and all-cause death) ($p = 0.024$). Recently, copeptin was found to be an independent predictive factor for total mortality but also a marker for general vulnerability, being influenced by the presence of HF, diabetes mellitus type 2, female sex and previous MI [68]. In previous research that assessed the relationship between copeptin and LV systolic function using a two-dimensional global longitudinal strain (GLS) in STEMI patients, based on the median copeptin level, it was found that there was a negative correlation between its values and early or 6 month GLS ($r = -0.45$ at the early stage; $r = -0.662$ at 6 months) [69]. In addition, according to Ersin and Ayca, it was found that onset copeptin levels were an independent predictor for contrast-induced nephropathy in patients with STEMI treated by PCI [64].

4. Biomarkers of Myocardial Necrosis

4.1. Platelet-Related Biomarkers

Platelets (PLTs) are small and anucleated cells that are derived from megakaryocytes secondarily to a maturation process that takes place in bone morrow. They are then re-leased into the bloodstream, where they have a limited lifespan of 5–7 days. They are multifunctional cells that play an essential role in primary hemostasis and thrombosis, addressing any hemorrhagic situations that appear at the level of the vascular endothelium or tissue as the result of an injury [70][71]. Furthermore, in the case of AMI, there tends to be a paradigm in which PLT can actually contribute to the formation of occlusive thrombosis as a consequence of plaque disruption [71]. Mean platelet volume (MPV) is an indirect, helpful, reliable and detectable indicator of platelet activity. Many studies demonstrate the correlation between MPV and MACEs in patients with ACS [72][73]. In retrospective research conducted by Avci et al. [74], the authors proved that an increased in-hospital MPV in STEMI patients undergoing PCI is an independent predictor factor of all-cause mortality (HR: 1.301, $p = 0.008$), MPV being measured upon admission and 2–3 days after. In a study that enrolled 1094 patients with ACS, Chang et al. [75] found that MPV was considerably greater in those with myocardial infarction than in the non-ACS group (8.6 ± 1.1 vs. 8.4 ± 1.0 fl, $p = 0.002$), high levels of MPV being associated with MACEs (all-cause mortality, recurrent ACS, target vessel reintervention and stroke). In particular, a retrospective study showed that high levels of MPV (MPV ≥ 9.0 fl) in patients with NSTEMI were associated with a substantial CAD ($p = 0.005$), defined as ≥ 1 major coronary artery stenosis (≥70%) [76]. In contrast with other researches, Çanga et al. [77] found no correlation between CRP and short-term prognosis in young patients with STEMI; only MPV (≥9.8 fl) was able to predict cardiovascular death and non-fatal reinfarction within 30 days upon admission ($p < 0.01$). Furthermore, greater mean platelet volume was identified as a predictor of death in patients with AMI throughout their hospitalization [78]. The primary objective of AMI therapy is to promptly revascularize the obstructed arteries by either fibrinolysis or pPCI, with the no-reflow

phenomena reducing the benefit of the second method and predicting negative outcomes. Hence, Kurtul and Acikgoz [79] proved the positive correlation between high MPV levels and no-reflow phenomena (MPV ≥ 8.65 fl). They illustrated that a cut-off value greater than 4.87 fl is a predictor of in-hospital mortality in comparison to those with lower cut-off levels (7.3% vs. 2.6%, $p < 0.001$). Recently, a meta-analysis that grouped 21 studies concluded that a higher MPV is associated with reduced post-intervention coronary flow (OR: 2.13, $p < 0.0001$) [80]. Moreover, in patients with STEMI treated with PCI, the MPV to platelet count (MPV/PC) ratio proved to be a predictor for long-term mortality and non-fatal reinfarction and, thus, a better prognostic marker than MPV alone [81][82].

4.2. Troponins

Troponins (T, I, C) (cTnT, cTnI, cTnC) are structure proteins that are implicated in actin–myosin interaction. They are produced and released from cardiomyocytes in response to increased stretch or necrosis. Hence, cTnT and cTnI, which are known as cardiac-specific troponins, have been proven to have and important role as a diagnostic marker for cardiac injury and AMI [31][83]. After an ACS, their levels rose within 2–4 h and reached a peak at 24 h, with a persistent elevated value for 2–3 weeks [84]. In ACS, time is precious and thus there is a need for a quick diagnostic tool to help guide treatment, such as these highly sensitive troponins (hs-cTnI and hs-cTnT). Zeljković et al., in a prospective study, presented mean values of cTnT ($p = 0.01$) together with peak levels of creatine kinase (CK) ($p = 0.0008$) as a long-term predictor of impaired LV systolic function < 50% in STEMI patients with preserved systolic function at onset and single-vessel coronary disease [85]. Along these lines, Mohammad et al. demonstrated in recent research on 578 STEMI patients undergoing PCI that hs-cTnT values were positively correlated with long-term LV systolic dysfunction (defined as LVEF ≤ 40% after one year), thus suggesting that this biomarker can be a useful instrument in identifying those patients at high risk of adverse cardiac remodeling [86]. However, the RUTI-STEMI real-life cohort study has not proven the prognostic role of new generations of troponins in STEMI [87]. Wanamaker et al. demonstrated that in-hospital mortality is increased in patients with high troponin upon admission, regardless of other clinical risk factors [88][89]. In a retrospective study of 818 patients with STEMI undergoing pPCI during the first day of the symptom's onset, both admission (HR: 1.08; $p < 0.001$) and peak post-procedural hs-cTnT levels (HR: 1.06; $p < 0.001$) were independently correlated with all-cause mortality over up to 3 years of follow-up [90]. Additionally, Harada et al. [91] has proven that greater post-procedural levels of hs-cTnT in patients with NSTEMI treated with early PCI are related to an increased risk of all-cause and cardiac death up to one year after the acute event. In contrast, there are data suggesting that high levels of cTnI post-pPCI do not predict three-year cardiovascular and all-cause mortality [60][92]. In addition, a recent meta-analysis concluded that raised cTn levels are an independent predictor factor for all-cause mortality in patients with ACS [93][94].

4.3. Creatin Kinase-MB (CK-MB)

Creatine kinase-MB (CK-MB), an isoenzyme of enzyme CK located mostly in cardiac cells, and in low levels in skeletal muscle, is released into circulation within 4–6 h after a cardiac injury, reaching a peak at 24 h and returning to normal after 48–72 h. In a Dutch study that enrolled 1360 STEMI subjects with a median follow-up period of 6.7 years, heart failure occurred in 85 patients (6.3%). Peak creatinine-kinase values, together with a left anterior descending artery culprit lesion, have been found to be an important predictor of heart failure development [95]. In

the same line, Yang et al. and Hendriks et al. proved the utility of an early measurement of CK-MB levels in predicting left ventricular adverse remodeling after an acute myocardial infarction and, thus, heart failure onset [96] [97]. A previous study that included more than 2000 NSTEMI patients treated with early PCI [98] revealed that peak post-procedural CK-MB (greater than three times the ULN cut-off) is an independent predictor of three-year mortality compared to lower levels of CK-MB. Other studies have shown that, in subjects with STEMI who underwent PCI, the CK-MB serum levels correlated with in-hospital mortality [99][100]. Furthermore, in a multivariate analysis, the incidence of contrast-induced nephropathy was substantially higher in those with increased CK-MB values when compared with the non-CIN group (p = 0.001) [101]. In addition, Hsu et al. [51] proved that, in patients with AMI, early peak CK-MB levels (cut-off 48.2 ng/mL) were associated with an increased risk for adverse cardiac remodeling within six months after discharge. Additionally, patients with log-transformed CK-MB values greater than 4.7 had a 3.4-fold higher incidence of CIN than those without [102]. Peak CK-MB showed a strong association with chronic scar dimension and chronic wall motion abnormality index in patients with non-transmural myocardial infarction undergoing PCI or coronary artery bypass graft surgery (CABG) [103].

4.4. Cystatin C (cysC)

Cystatin C (cysC) is a pleiotropic cysteine protease inhibitor that regulates cathepsins S and K in human vascular pathology, being a part of the catabolism processes of most proteins in nucleated cells. In normal conditions, cysC is an indicator of renal function, with greater sensitivity than serum creatinine for incipient stages of renal function. It could also be present in cardiomyocytes, showing an important increase in a hypoxic scenario [104][105][106]. It is also known that cysC is part of processes such as aging, apoptosis, destruction of proteins in the extracellular matrix, cell differentiation and proliferation and synthesis of oxide nitric (NO) [107]. In AMI, the prognostic significance of cysC may be attributable to multiple underlying mechanisms. First, it has been suggested that cysC plays an active role in the physiopathological process of atherosclerosis plaque formation. Furthermore, being an endogenous cathepsin inhibitor, it maintains the balance between proteases and their principal inhibitor. An increased level indicates the disruption of this relationship, therefore accelerating atherosclerosis development [108]. Secondly, elevated cysC values may lead to no-reflow phenomena due to its correlation with impaired renal function and inflammation, which are associated with oxidative stress, microvascular endothelial dysfunction, pro-coagulant cytokines and free radicals. Therefore, this biomarker is a useful predictor for no-reflow events in STEMI patients treated with pPCI [109]. Recently, Lou et al. [110] presented cysC levels at admission as a biomarker of cardiac function, and they showed a negative relationship with the ejection fraction value (p < 0.0001) and functioned as a predictor for MACEs, cardiovascular mortality and all-cause mortality in AMI patients within 4 years of follow-up. In addition, elevated levels of cysC measured at any stage within the first year after an ACS positively correlated with the composite endpoint (cardiac mortality, non-fatal AMI and unplanned coronary revascularization) (p = 0.006). Further, the 12th to 14th day measurements demonstrate an important predictive role regarding adverse cardiovascular outcomes within 3 years of follow-up [111][112]. On the same note, a meta-analysis conducted by Chen et al. [105] suggested that increased serum cysC levels positively correlated with a higher risk of MACEs and mortality in patients with STEMI undergoing PCI. Similarly, there are data that present cysC as a predictor of negative cardiovascular events, such as cardiovascular death, hospitalization for HF, recurrent cardiovascular events and the severity of vascular lesions, with cysC being strongly correlated with the Gensini

score (p < 0.05) in acute coronary syndrome patients [113][114][115][116]. Even if the retrospective study conducted by Chen et al. [117] included subjects with elevated cysC levels who were older and had hypertension, advanced Killip classes and a reduced eGFR, after adjustment for these confounders, this biomarker was found to be an independent predictor for negative cardiovascular outcomes and death in STEMI patients treated with late PCI (more than 7 days from symptom onset). In contrast with the aforementioned study, a sub-analysis of the HIJ-PROPER demonstrated that levels of cysC greater than 1.03 mg/L are independent predictors only for all-cause mortality but not for cardiovascular events [118]. In addition, in a cohort of patients with STEMI undergoing pPCI, plasmatic cysC did not predict acute kidney injury, one-year mortality or hemodialysis necessity after one year [119].

4.5. Heart-Type Fatty Acid Binding Protein (H-FABP)

Heart-type fatty acid binding protein (H-FABP) is a cytoplasmatic protein involved in the metabolism of fatty acid in the myocardium. Its level increases promptly (< one hour) during a myocardial injury, with a peak at 4–6 h and return to baseline after 24 h [120]. Therefore, as it is detectable in plasma before cTn, it can be considered an early biomarker of AMI and a useful tool in reinfarction prediction [121][122]. The association between H-FABP and stable coronary heart disease has been reported in several studies as an independent predictor for cardiovascular events and acute HF-related hospitalization. A group of patients with high H-FABP levels had a 1.5-fold higher rate of negative outcomes than the lowest-level group [123][124]. Even if H-FABP is quickly released into the bloodstream and is a stable and soluble heart tissue-specific protein with high concentration in myocardium, there are no recent data regarding its prognostic value [120]. However, there are some reviews in which H-FABP seemed to have some prognostic value for patients with acute coronary syndrome, but supplementary studies are needed to evaluate whether there is a correlation between this and adverse outcomes [125][126].

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