EDITORIAL

Increased red blood cell distribution width and platelet-to-lymphocyte ratio for predicting all-cause mortality in patients with type 2 diabetes and advanced heart failure: a causal association or epiphenomenon?

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Growing evidence indicates that there is a synergistic negative effect of type 2 diabetes and heart failure (HF) on the risk of all-cause mortality and other adverse clinical outcomes. An updated systematic review and meta-analysis of 43 randomized controlled trials and registries,[1] involving a total of nearly 380 000 patients with acute or chronic HF, has clearly shown that the presence of type 2 diabetes adversely affects long-term survival and risk of hospitalization in patients with acute and chronic HF. Indeed, the presence of diabetes alone increased the risk of all-cause mortality by 28%, the risk of cardiovascular mortality by 34%, the risk of hospitalization by 35%, and the combined end-point of all-cause mortality or hospitalization over a median follow-up period of 3 years by 41%. The adverse impact of diabetes on the risk of mortality and hospitalization was higher in patients with chronic HF than in those with acute HF.

On the other hand, it is also well known that patients with type 2 diabetes are at higher risk of developing HF over time.[2] In a recent meta-analysis of 15 cross-sectional studies,[3] involving a total of 2070 individuals (877 patients with type 2 diabetes and 1193 controls), it has been also emphasized that early left ventricular diastolic dysfunction is nearly 2-fold greater in patients with type 2 diabetes than in individuals without diabetes. Due to the especially unfavorable impact of concomitance of diabetes and HF on mortality risk, and also considering the possibility of establishing effective pharmacologic treatments for these 2 pathologic conditions, the early identification of new risk factors will become crucial in identifying patients at higher risk of adverse clinical outcomes.

In an article published in this issue of *Kardiologia Polska* (*Kardiol Pol*), Siedlecki et al[4] retrospectively analyzed the clinical and laboratory data of 367 consecutive hospitalized patients with type 2 diabetes and advanced HF, with the aim of identifying potential risk factors of all-cause mortality over a mean follow-up of 4.4 years.[4] In the multivariable Cox regression analysis, the risk of all-cause mortality was found to be 60% higher in patients with permanent atrial fibrillation, approximately 5% higher in those with increased values of red blood cell distribution width (RDW), and approximately 1% higher in those with increased values of platelet-to-lymphocyte ratio (PLR). Notably, although the independent contribution of both RDW and PLR in predicting all-cause mortality was modest (ie, approximately 5%), no other clinical parameters could independently predict the risk of mortality in these hospitalized patients with diabetes and advanced HF.

The results of this interesting study are not really unexpected but deserve further scrutiny. The fact that atrial fibrillation substantially increases the risk of all-cause mortality in patients

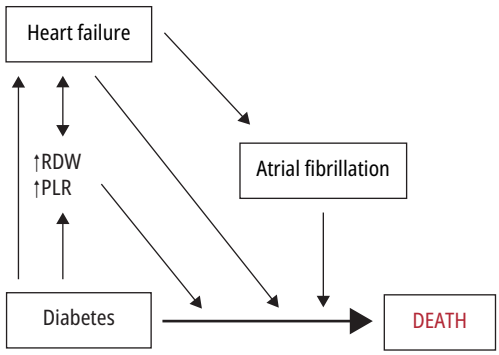

FIGURE 1 Possible biological and clinical interconnections between type 2 diabetes, heart failure, atrial fibrillation, and increased red blood cell distribution width (RDW) and platelet-to-lymphocyte ratio (PLR)

with type 2 diabetes and HF is well known, and is also biologically plausible since atrial fibrillation, type 2 diabetes, and HF share some molecular pathways, such as chronic inflammation, oxidative damage, and increased generation of advanced glycosylation end products.[5]

More intriguing evidence is instead visible in RDW and PLR data. An important take-home message that can hence be derived from the study by Siedlecki et al[4] is that 2 simple hematological parameters, such as RDW and PLR, may independently predict the risk of all-cause mortality in patients with type 2 diabetes and advanced HF. Red blood cell distribution width, reported either as a standard deviation of erythrocyte volumes or as a percent value, is directly measured (or calculated) by the vast majority of modern hematologic analyzers, and is then automatically included in laboratory reports.[6] Unlike RDW, PLR is not currently reported by hemocytometer analyzers, but its value can be easily calculated from the total number of platelets and lymphocytes available in the laboratory information system, and can hence be included in the laboratory reports. Nevertheless, the most important and still unresolved issue is whether an increased value of RDW or PLR in patients with diabetes and HF, who are at higher risk of all-cause mortality, shall be considered as a causal risk factor, a simple epiphenomenon (ie, a risk marker), or rather an innocent bystander. As far as we are concerned, all these 3 hypotheses might hold true (as schematically reported in FIGURE 1).

It has been shown that erythrocyte structure and biology deeply interplay with the risk of developing both HF and atrial fibrillation, whereby an increased value of RDW (which reflects anisocytosis) is frequently associated with chronic inflammation, myocardial ischemia, increased oxidative stress, and impaired blood flow through the microcirculation.[7,8] Similar evidence has been supplied for PLR, since both platelets and lymphocytes are directly involved in the pathophysiology of cardiovascular disease and HF, but may also indirectly contribute to the development of an arrhythmogenic substrate by establishing a prothrombotic milieu and impairing vascular repair.[9] Regarding the possible interpretation of either an increased RDW or increased PLR value as simple risk markers of mortality, also this hypothesis appears to be plausible, since the presence of diabetes[10] and the gradual deterioration of cardiac function[11] may exert adverse effects on bone marrow function. It is hence plausible to assume that an increased value of either RDW or PLR may be a direct consequence of these 2 conditions. Finally, it cannot be ruled out that increased values of RDW and PLR shall be seen as innocent bystanders, while many risk factors involved in the pathogenesis of type 2 diabetes, HF, and atrial fibrillation may also trigger bone marrow abnormalities.

Therefore, following this line of reasoning, we strongly believe that further larger prospective studies with longer follow-up periods will be needed to definitely establish the biological and clinical significance of increased values of RDW and PLR in this clinical setting, as well as to define whether these 2 hemocytometer parameters may be ready for prime time for predicting all-cause and cardiovascular mortality in patients with type 2 diabetes and advanced HF.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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