

Cardiovascular Morbidity and Mortality in Rheumatoid Arthritis

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Received: May 31, 2019; **Published:** June 27, 2019

Rheumatoid arthritis is an autoimmune inflammatory rheumatic disease that causes chronic synovial inflammation eventually leading to joint destruction and disability [1]. Many studies have reported an increased risk of morbidity and mortality in patients with rheumatoid arthritis (RA), largely attributable to cardiovascular (CV) events [1,2]. The contribution of traditional risk factors and RA disease characteristics to this mortality has been uncertain, in particular, given the recent appreciation of the important role of inflammatory processes in the development and progression of atherosclerosis.

RA is the consequence of a persistent imbalance between pro- and anti-inflammatory immune mechanisms, leading to chronic inflammation. Shrivastava, et al. (2015) demonstrate that RA patients have high levels of inflammatory markers which suggest a possible role of high sensitive C-reactive protein (CRP) and cytokines in the pathogenesis and increased risk for CV disease in RA [3]. Traditional and RA-specific risk factors to this increased risk of CV morbidity and mortality did not fully explain the increased CV mortality observed in RA [4]. As a systemic inflammatory disease, patients with RA have 60% increase risk for CV disease compared with the general population [5]. Sherine, et al. (2008) observed a significantly increased risk of overall mortality, CV death, ischemic heart disease, and heart failure compared with the general population in a population-based incidence cohort of RA patients followed up for approximately 15 years [2]. Maradit-Kremers, et al. (2005) after adjustment for demographics, and traditional CV risk factors found that higher erythrocyte sedimentation rate (ESR), small and large joint swelling, rheumatoid nodules, vasculitis, RA lung disease and endothelial dysfunction, were all independently associated with an increased risk of CV death [6].

Endothelial dysfunction often precedes manifest atherosclerosis. Both traditional, Framingham risk factors and inflammation-associated factors are involved in RA-associated atherosclerosis. Arterial stiffness is a useful marker of the extent of atherosclerosis in the abdominal aorta. Presented as pulse wave velocity (PWV), the arterial stiffness is strongly associated with atherosclerosis at various sites in the vascular tree. Many studies demonstrated increased arterial stiffness in patients with RA free from CV risk factors and overt CV disease, secondary to the effect of inflammatory process associated with RA [6,7]. There are a small number of studies that examined and compare the aortic stiffness in RA patients with aortic stiffness in the general population (GP) [8,9]. We compared the aortic stiffness in patients with RA and patients from general population [8] and we found increased aortic PWV (stiffness) or reduced arterial elasticity in patients with RA compared with lower PWV in GP, occurring independently of traditional risk factors.

In the progression of arterial stiffness in the GP group especially in elderly, only the traditional risk factors (hypertension, diabetes mellitus, smoking, obesity and dyslipidemia) were evident. Unlike them, in patients with RA, arterial stiffness is accelerated owing to synergism between age and traditional risk factors plus nontraditional factors (factors related to the RA: inflammatory markers CRP, ESR and serum albumin, disease activity scores, seropositivity, physical disability, etc [8,10]. If the wall of the aorta stiffens, pulse pressure

increases. Thus, pulse pressure is a widely accessible, if imperfect, indicator of arterial stiffness. The higher pulse pressures are associated with a moderate increase in the risk for major CV disease events, such as myocardial infarction, heart failure, arrhythmia and stroke [11].

We continued before started 2-year comparative study for the next period, in total to 48-months, to estimate survival rate in RA patients [8]. We measured PWV and we registered the mean survival time in 8 (10%) deceased patients (45.26 ± 8.7 months). These are unpublished results from before published study [8]. A plot of the Kaplan-Meier estimate of the survival function presents as series of horizontal steps of declining magnitude, approaching the true survival function in RA patients is shown in figure 1. Vertical drop indicates a CV event.

The mean PWV in deceased patients was 10.2 ± 1.4 m/s vs. 7.9 ± 1.1 m/s in survived RA patients. There is a high statistical significance between PWV in survived and in deceased patients. Comparing the PWV results in survivors (7.9 ± 1.1 m/s) and non-survivors (10.2 ± 1.4 m/s), we got significantly ($p < 0.0001$) higher PWV in deceased patients. PWV in deceased patients from cardiovascular disease is more

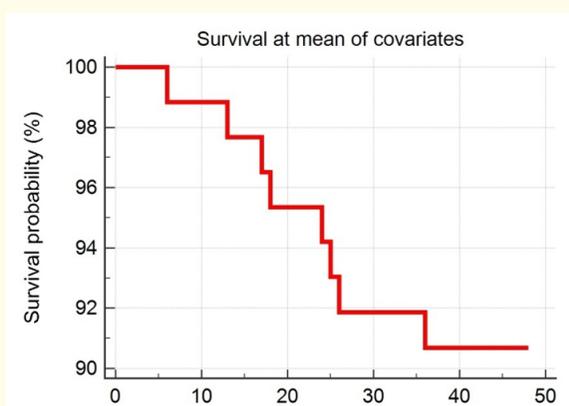


Figure 1: Kaplan Meier survival analyses in 48-months follow up period.

pronounced: it is equal to 10.2 ± 1.4 m/s, which means stiffer aorta in Ra patients with CV event. At first sight, it is not very big difference, only about 2.3 m/s. But, if we know the fact, that an increase of aortic PWV by 1 m/s corresponds to a risk increase of 15% in CV mortality, the above mentioned fact is not for underestimation [12].

In Cox-regression analysis we calculate regression coefficient [$b = 0.4063$], hazard ratio coefficient $\text{Exp}[b] = 1.5013$, Wald = 0.9779, p value = 0.032, standard error [SE] = 0.41 and 95% CI [confidence interval] of $\text{Exp}[b]$ of independent predictor (PWV) for cardiovascular mortality in 4-year follow-up period. PWV as covariate with positive regression coefficient is associated with increased hazard and decreased survival times. The predictor for CV mortality, PWV has an $\text{Exp}(b)$ hazard ratio (HR) coefficient of 1.5013 that mean the hazard ratio (HR) increases by 1.5013 (50.913%) with each unit increase in PWV. I am really sure that Cox-regression results will get more pronounced HR coefficient if we include more RA patients with prolonged follow-up period. This would further confirm the impact of arterial stiffness, which is significantly higher in RA patients as one of the potential reasons for increase of CV mortality in RA patients.

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Volume 10 Issue 7 July 2019

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