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The role of neutrophil-to-lymphocyte ratio in men with erectile dysfunction—preliminary findings of a real-life cross-sectional study

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SUMMARY

The aim of this study was to investigate the role of systemic inflammation by means of the neutrophil-to-lymphocyte ratio (NLR) in men with erectile dysfunction (ED). Complete demographic, clinical, and laboratory data from 279 consecutive men with newly diagnosed ED were analyzed. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI). A complete blood count was requested for every man, and the NLR was calculated for every individual. Patients were invited to complete the IIEF questionnaire. Logistic regression models tested the odds (OR, 95% CI) of severe ED (defined as IIEF-EF <11, according to Cappelleri's criteria) after adjusting for age, BMI, comorbidities (CCI >0), metabolic syndrome, NLR, cigarette smoking, and color duplex Doppler ultrasound parameters. Likewise, LNR values were also dichotomized according to the most informative cutoff predicting severe ED using the minimum *p* value approach. Median [IQR] age of included men was 51 [40–64] years. Of all, 87 (31%) men had severe ED. Men with severe ED were older (median [IQR] age: 61 [47–67] vs. 49 [39–58] years) and had a higher rate of CCI>0 [46/87 (53%) vs. 44/192 (23%) patients]. Thereof, NLR was dichotomized according to the most informative cutoff (NLR>3); patients with severe ED more frequently had NLR>3 as compared to all other ED patients [namely, 18/87 (21%) vs. 13/192 (7%)]. At multivariable logistic regression analysis, NLR>3.0 emerged as an independent predictor (OR [CI] 2.43 [1.06; 5.63]) of severe ED, after accounting for other clinical variables. A NLR>3 increased the risk of having severe ED in our cohort, boosting the already existing evidence linking systemic inflammation to ED. Moreover, this easily obtainable index can be clinically useful in better risk-stratifying patients with ED.

INTRODUCTION

Erectile dysfunction (ED) was recently proposed as a proxy of general health status (Salonia *et al.*, 2012). More specifically, a worse erectile function is associated with a lower general health status in men with ED (Salonia *et al.*, 2012). ED may significantly increase the risk of cardiovascular disease (CVD), coronary heart disease, stroke, overall atherosclerotic cardiovascular events (Batty *et al.*, 2010; Dong *et al.*, 2011). Despite this, ED severity was shown to be associated with overall men's health, even irrespective of cardiovascular risk factors (Capogrosso *et al.*, 2017). Metabolic disorders, cardiovascular comorbidities, and ED are closely related, sharing several pathophysiological factors, including systemic low-grade inflammation (Vlachopoulos *et al.*, 2007). Erectile function was shown to decline as a function of increasing peripheral blood inflammatory markers, such as fibrinogen, interleukin-6, and high-sensitivity C-reactive protein (Vlachopoulos *et al.*, 2007). Among the several available markers of systemic inflammation, the neutrophil-to-lymphocyte ratio (NLR) was shown to be prognostically associated with several oncologic, cardiovascular, and inflammatory diseases (Cho *et al.*, 2011; Chandrashekara *et al.*, 2015; Nishida *et al.*, 2017). However, despite the biological connection between inflammation and ED, NLR role was never inquired in ED patients. Therefore, we aimed at evaluating the prognostic role of NLR in a cohort of white European men evaluated at a single academic center for new-onset ED.

METHODS

Study population

The analyses of this cross-sectional study were based on a cohort of 279 consecutive white European men consecutively assessed at a single academic center for new-onset ED between

November 2015 and November 2016. Patients were enrolled if they were ≥ 18. Patients were evaluated with a thorough self-reported medical history, including age and comorbidities. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI) (Charlson *et al.*, 1987). We used the International Classification of Diseases 9th revision because its coding algorithms were used to define the 17 comorbidities that constitute the most widely used CCI score. For the aim of the analysis, CCI was categorized as 0 and ≥1. Body mass index (BMI), defined as weight in kilograms by height in square meters, was measured for every patient.

For the specific purpose of this study, ED was defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance (Yafi *et al.*, 2016); moreover, patients were enrolled if they failed at least 50% of four consecutive attempts at sexual intercourse. Likewise, to provide a frame of reference for objectively interpreting psychometric data on sexual functioning, patients were invited to complete the International Index of Erectile Function (IIEF) (Rosen *et al.*, 1997). To interpret ED severity, we used the IIEF-Erectile Function (IIEF-EF) domain classification as proposed by Cappelleri *et al.*, (1999). Consequently, severe ED was defined as a IIEF-EF score <11. Moreover, every patient underwent standardized penile color duplex Doppler ultrasound (CDDU) assessment (Sikka *et al.*, 2013). Venous blood samples were drawn from each patient, and a complete blood count was executed for every man at study entry at the same laboratory at the time of admission, thus including total and differential white blood cell (WBC) counts. Total counts for WBC, neutrophils, and lymphocytes were assessed using an automated blood cell counter. NLR was calculated as the ratio of the neutrophil to lymphocyte counts.

Data collection was performed following the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to deliver their own anonymous information for future studies.

Statistical analyses

Data are reported as medians and interquartile range (IQR). The statistical analyses consisted of several steps. First, the relationship between NLR and ED severity was graphically explored using the locally weighted scatterplot smoothing (lowess) method to account for possible nonlinear relationship (Bennette & Vickers, 2012). Second, NLR values were dichotomized according to the most informative cutoff value for the outcome IIEF-EF<11 (namely, severe ED) using the minimum p value approach, as described by Mazumdar & Glassman, (2000). Third, univariable (UVA) and multivariable (MVA) logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (95% CIs) for the severe ED outcome, including as model covariates NLR, age at diagnosis, BMI, cigarette smoking, comorbidities as scored with the CCI, metabolic syndrome (MetS), mean cavernosal peak systolic velocity (PSV) bilaterally evaluated at penile color duplex Doppler 20 min after intracavernosal PGE1 injection, and venogenic ED defined according to Sikka *et al.*, (2013).

RESULTS

Table 1 details descriptive statistics of the whole study cohort as stratified by ED severity. Overall, severe ED was found in 87 of 279 (31%) men. Median [IQR] age was 51 years (40–64), BMI 25 kg/m^2 [23–27], and NLR 1.7 [1.3–2.3]. Compared to men with non-severe ED, men with severe ED were older (median [IQR] age 61 [47–67] vs. 49 [39–58] years) and had a higher rate of CCI>0 (46/87 (53%) vs. 44/192 (23%)) (Table 1).

Table 1 Characteristics of the study cohort stratified by ED severity

	IIEF-EF < 11 *n* = 87	IIEF-EF = >11 *n* = 192	Overall *n* = 279
Age			
Median (IQR)	61 (47–67)	49 (39–58)	51 (40–64)
BMI			
Median (IQR)	26 (24–28)	25 (23–27)	25 (23–27)
CCI > 0			
0	41 (47)	148 (77)	189 (68)
1+	46 (53)	44 (23)	90 (32)
MetS			
No	44 (51)	154 (80)	198 (71)
Yes	43 (49)	38 (20)	81 (29)
Cigarette smoking			
No	68 (78)	142 (74)	210 (75)
Yes	19 (22)	50 (26)	69 (25)
NLR			
Median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)
NLR > 3			
No	69 (79)	179 (93)	248 (89)
Yes	18 (21)	13 (7)	31 (11)

BMI, body mass index; CCI, Charlson Comorbidity Index; IIEF-EF, International Index of Erectile Function-Erectile Function domain; MetS, metabolic syndrome; NLR, neutrophil-to-lymphocyte ratio.

The most informative cutoff value for NLR in predicting severe ED was 3 (p = 0.02; Youden index: 14%). Although median NLR values were similar in men with or without severe ED, the proportion of NLR>3 among men with severe ED was 18/87 (21%) vs. 13/192 (7%) in the remaining cohort.

Figure 1 displays the inverse relationship between ED severity and NLR; in the context, the higher the NLR values, the worse the IIEF-EF domain scores.

Table 2 details UVA and MVA logistic regression models for the outcome 'severe ED'. At univariable analysis, age (OR [95% CI]: 1.04 [1.02–1.07]), the presence of comorbidities (CCI>0, 3.77 [2.21–6.51]), MetS (OR [95% CI]: 3.96 [2.29–6.91]), venogenic ED (OR [95% CI]: 2.92 [1.67–5.13]), low PSV (OR [95% CI]: 0.92 [0.89–0.96]), and NLR>3 (3.59 [1.68–7.87]) increased the probability of having severe ED. At multivariable analysis, only NLR>3 (2.43 [1.06–5.63]) and PSV (OR [95% CI]: 0.98 [0.96–0.99]) achieved independent predictor status for severe ED.

DISCUSSION

In this cross-sectional study, we inquired whether low-grade systemic inflammation, quantified by means of NLR, was associated with worse erectile function in men with ED. High NLR values, >3 according to the most informative cutoff found at our analyses, were associated with an increased risk of severe ED, even after accounting for known and established risk factors for ED.

The current findings are in agreement with the hypothesis linking low-grade systemic inflammation to ED (Vlachopoulos *et al.*, 2007). Low-grade systemic inflammation is an important element of the association between metabolic syndrome, ED, and CAD (Vlachopoulos *et al.*, 2007). Several blood-derived inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), interleukin-1 beta, interleukin-6 (IL-6), and tumor

Figure 1 st-lowess curve exploring the relationship between NLR and ED severity. NLR, neutrophil-to-lymphocyte ratio. [Colour figure can be viewed at wileyonlinelibrary.com]

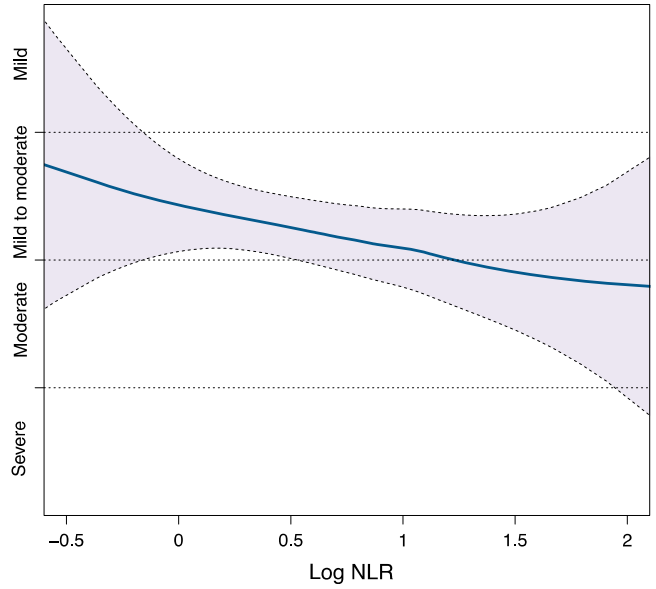

Table 2 Logistic regression models with odds ratios (OR) and 95% confidence intervals (CIs) for the outcome 'severe ED'

	n (events)	UVA		MVA	
		OR	95% CI	OR	95% CI
NLR>3					
No	248 (69)	1.00	(Ref.)	1.00	(Ref.)
Yes	31 (18)	3.59	1.68–7.87	2.43	1.06–5.63
Age					
Years		1.04	1.02–1.07	1.02	0.99–1.05
BMI					
kg/m^2		1.06	0.99–1.13	0.99	0.91–1.08
CCI					
0	189 (41)	1.00	(Ref.)	1.00	(Ref.)
1+	90 (46)	3.77	2.21–6.51	1.58	0.71–3.45
MetS					
No	198 (44)	1.00	(Ref.)	1.00	(Ref.)
Yes	81 (43)	3.96	2.29–6.91	2.08	0.90–4.89
Cigarette smoking					
No	210 (68)	1.00	(Ref.)	1.00	(Ref.)
Yes	69 (19)	0.79	0.43–1.43	1.06	0.54–2.02
Venogenic ED					
No	208 (52)	1.00	(Ref.)	1.00	(Ref.)
Yes	71 (35)	2.92	1.67–5.13	1.30	0.57–2.94
PSV at 20′					
cm/sec		0.92	0.89–0.96	0.98	0.96–0.99

BMI, body mass index; CCI, Charlson Comorbidity Index; ED, erectile dysfunction; IIEF-EF, International Index of Erectile Function-Erectile Function domain; MetS, metabolic syndrome; NLR, neutrophil-to-lymphocyte ratio; PSV, peak systolic velocity.

necrosis factor alpha (TNF-α), were shown to be inversely correlated to SHIM score in men with ED (Vlachopoulos *et al.*, 2006). Moreover, hs-CRP and IL-6 levels were found higher in men with ED compared to ED-free controls (Chiurlia *et al.*, 2005; Vlachopoulos *et al.*, 2006).

Overall, NLR is a widely used prognostic index, with applications in oncological, cardiovascular, and inflammatory diseases (Cho *et al.*, 2011; Chandrashekara *et al.*, 2015; Nishida *et al.*, 2017). Several cutoffs have been proposed, according to the different fields of interest, generally ranging between 2 and 5 (Cho *et al.*, 2011; Chandrashekara *et al.*, 2015; Nishida *et al.*, 2017). To the best of our knowledge, this is the first study exploring the role of NLR in men with ED.

The link between ED and comorbidities is well-known (Salonia *et al.*, 2012). Erectile dysfunction was shown to anticipate a clinically manifest CAD in a relevant proportion of men (Montorsi *et al.*, 2003) and now is recognized as a major risk factor for development of CAD and cardiovascular events (Guo *et al.*, 2010; Vignozzi *et al.*, 2012; Yamada *et al.*, 2012; Vlachopoulos *et al.*, 2013). Moreover, ED is recognized as a sentinel of general health status, both considering and irrespective of cardiovascular comorbidities (Salonia *et al.*, 2012; Capogrosso *et al.*, 2017). Therefore, it is of paramount clinical relevance to identify men at risk of both future cardiac events and health status decline. As several inflammatory biochemical markers were extensively shown to be predictors of future cardiovascular outcomes (Danesh *et al.*, 2005; Lowe, 2005), the clinical significance of NLR in men with ED may be glaring. Previous studies have found that the NLR is a reliable inflammatory biomarker for the atherosclerotic process and is associated with several clinical cardiovascular outcomes (Brown *et al.*, 2001; Horne *et al.*, 2005). More specifically, a NLR >3.86, as part of a more complex prognostic score, was associated with an increased 6-mos mortality in men who experienced ST-elevation myocardial infarction (STEMI) (Cho *et al.*, 2011). More recently, a NLR >3.90 was associated with an increased microcirculatory resistance in men with STEMI, that is, an index of microvascular function.

Several of the pathophysiological mechanisms acting together with low-grade systemic inflammation in fostering both ED and cardiovascular diseases can be intercepted by the NLR. Neutrophils produce and secrete several inflammatory mediators (e.g., myeloperoxidase or MPO, reactive oxygen species), which can be responsible of both myocardial and non-myocardial tissue damages (Hansen, 1995; Nishida *et al.*, 2017). At this regard, neutrophil-secreted MPO levels were found to be significantly higher in men with arteriogenic ED vs. control individuals and non-arteriogenic ED patients (Dozio *et al.*, 2013). Conversely, lymphocytes may have a regulatory action on neutrophils (Zhang *et al.*, 1992). The ratio between high neutrophils and low lymphocytes is thought to simultaneously and better depict the role of these two white blood cell subpopulations, conveying a more thorough information than what could be obtained by focusing on neutrophils alone (Azab *et al.*, 2010). Endothelial dysfunction is a further relevant component in the pathogenesis of ED (Kaiser *et al.*, 2004; Yafi *et al.*, 2016). Endothelial dysfunction is not a local phenomenon of the corpora cavernosa, as men with ED were shown to have endothelial dysfunction in other districts as well, even before the development of other overt functional or structural systemic vascular disease (Kaiser *et al.*, 2004; Vardi *et al.*, 2009). These findings are substantiated by clinical studies suggesting that cavernosal arteries blood flow is inversely associated with the risk of experiencing major cardiovascular events (Corona *et al.*, 2008, 2010).

Moreover, ED independently predicted endothelial dysfunction among middle-aged men presenting for wellness screening (Peyton *et al.*, 2016). An association between NLR and endothelial dysfunction was previously reported in men with pulmonary thromboembolism (Kurtipek *et al.*, 2017).

As a whole, high NLR emerges as an epiphenomenon of a plethora of factors contributing to ED onset and maintenance, thus involving inflammation, vascular alterations, tissue damage, and endothelial dysfunction. Nonetheless, a pro-inflammatory hormonal milieu could alter both erectile function and NLR (Vignozzi *et al.*, 2012). The possible role of NLR in capturing all these features makes it a powerful candidate marker for assessment of both sexual health and cardiovascular risk in male patients; thereof, further studies are definitely needed at this regard, as well as for the female counterpart (Vignozzi *et al.*, 2012).

Our study is not devoid of limitations. First, this was a hospital-based study, raising the possibility of a number of selection biases. Patients were recruited from a single tertiary referral academic outpatient clinic; therefore, larger studies across different centers and populations will be needed to substantiate our findings. Second, the cross-sectional design does not allow to draw conclusions on the overall diagnostic role of NLR in ED due to the lack of same-race, age-matched cohort of healthy controls. Third, this analysis did not take into account other IIEF domains, thus including sexual desire and intercourse satisfaction. Likewise, we did not assess rates of depression or anxiety using validated psychometric tools. Fourth, we decided not to include androgen status and the hormonal milieu because not every patient had a complete laboratory tests profile at his first office visit, which was actually an entry criterion for this study; however, in the subcohort of men with available total testosterone values (n = 174), NLR >3 was still associated with severe ED at multivariable analysis adjusted for testosterone levels (OR [95% CIs] 3.47 [1.10–11.68]). Strengths of this study include the precise assessment of both ED at diagnosis and of patient-related comorbidities at an academic outpatient clinic, as well as the use of a unique centralized test laboratory for the execution of blood tests.

CONCLUSIONS

This exploratory analysis examined for the first time the role of NLR in men with ED. We found that NLR decreases as a function of increasing ED severity. Moreover, we identified NLR >3 as the most informative cutoff for identifying men with severe ED, defined as IIEF-EF score <11. Men with severe ED had a tripled rate of NLR >3 compared to men with non-severe ED. After accounting for established risk factors for decreased erectile function (i.e., older age, comorbidities, obesity, and cigarette smoking), NLR values >3 emerged as an independent predictor of severe ED. The easy availability of this index in the everyday clinical practice, as well as its ability in capturing several aspects of ED pathogenesis, makes NLR a possible candidate for ED risk assessment and stratification.

REFERENCES

Azab B, Torbey E, Hatoum H, Singh J, Khoueiry G, Bachir R, McGinn JT Jr, McCord D & Lafferty J. (2010) Usefulness of neutrophil to lymphocyte ratio in predicting short-and long-term mortality after NonST-elevation myocardial infarction. *Am J Cardiol* 106, 470–476.

Batty GD, Li Q, Czernichow S, Neal B, Zoungas S, Huxley R, Patel A, de GB, Woodward M, Hamet P & Harrap SB. (2010) Erectile dysfunction and later cardiovascular disease in men with type 2 diabetes: prospective cohort study based on the ADVANCE (Action in Diabetes and Vascular Disease: preterax and Diamicron Modified-Release Controlled Evaluation) trial. *J Am Coll Cardiol* 56, 1908–1913.

Bennette C & Vickers A (2012) Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. *BMC Med Res Methodol* 12, 21.

Brown DW, Giles WH & Croft JB. (2001) White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. *J Clin Epidemiol* 54, 316–322.

Capogrosso P, Ventimiglia E, Boeri L, Capitanio U, Gandaglia G, Dehò F, Pederzoli F, Cazzaniga W, Scano R, Montorsi F & Salonia A. (2017) Sexual functioning mirrors overall men's health status, even irrespective of cardiovascular risk factors. *Andrology* 5, 63–69.

Cappelleri JC, Rosen RC, Smith MD, Mishra A & Osterloh IH. (1999) Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology* 54, 346–351.

Chandrashekara S, Rajendran A, Jaganath AB & Krishnamurthy R. (2015) Neutrophil-lymphocyte ratio, pain perception, and disease activity score may serve as important predictive markers for sustained remission in rheumatoid arthritis. *Reumatismo* 67, 109–115.

Charlson ME, Pompei P, Ales KL & MacKenzie CR. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373–383.

Chiurlia E, D'Amico R, Ratti C, Granata AR, Romagnoli R & Modena MG. (2005) Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. *J Am Coll Cardiol* 46, 1503–1506.

Cho KH, Jeong MH, Ahmed K, Hachinohe D, Choi HS, Chang SY, Kim MC, Hwang SH, Park KH, Lee MG & Ko JS. (2011) Value of early risk stratification using hemoglobin level and neutrophil-to-lymphocyte ratio in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 107, 849–856.

Corona G, Fagioli G, Mannucci E, Romeo A, Rossi M, Lotti F, Sforza A, Morittu S, Chiarini V, Casella G & Di GP. (2008) Penile doppler ultrasound in patients with erectile dysfunction (ED): role of peak systolic velocity measured in the flaccid state in predicting arteriogenic ED and silent coronary artery disease. *J Sex Med* 5, 2623–2634.

Corona G, Monami M, Boddi V, Cameron-Smith M, Lotti F, De VG, Melani C, Balzi D, Sforza A, Forti G & Mannucci E, (2010) Male sexuality and cardiovascular risk. A cohort study in patients with erectile dysfunction. *J Sex Med* 7, 1918–1927.

Danesh J, Lewington S, Thompson SG, Lowe G, Collins R, Kostis J, Wilson AC, Folsom AR, Wu K, Benderly M & Goldbourt U. (2005) Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 294, 1799–1809.

Dong J-Y, Zhang Y-H & Qin L-Q. (2011) Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 58, 1378–1385.

Dozio E, Barassi A, Marazzi MG, Vianello E, Colpi GM, Solimene U, Melzi GD & Corsi MR. (2013) Plasma myeloperoxidase in patients with erectile dysfunction of arteriogenic- and non-arteriogenic origin: association with markers of endothelial dysfunction. *J Biol Regul Homeost Agents* 27, 749–755.

Guo W, Liao C, Zou Y, Li F, Li T, Zhou Q, Cao Y & Mao X. (2010) Erectile dysfunction and risk of clinical cardiovascular events: a meta-analysis of seven cohort studies. *J Sex Med* 7, 2805–2816.

Hansen PR. (1995) Role of neutrophils in myocardial ischemia and reperfusion. *Circulation* 91, 1872–1885.

Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, Renlund DG & Muhlestein JB. (2005) Which white blood cell subtypes predict increased cardiovascular risk? *J Am Coll Cardiol* 45, 1638–1643.

Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL & Bank AJ. (2004) Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 43, 179–184.

Kurtipek E, Büyükterzi Z, Büyükterzi M, Alpaydın MS & Erdem SS. (2017) Endothelial dysfunction in patients with pulmonary

thromboembolism: neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. *Clin Respir J* 11, 78–82.

Lowe GDO. (2005) Circulating inflammatory markers and risks of cardiovascular and non-cardiovascular disease. *J Thromb Haemost* 3, 1618–1627.

Mazumdar M & Glassman JR. (2000) Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. *Stat Med* 19, 113–132.

Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, Galli S, Ravagnani PM & Montorsi P. (2003) Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 44, 360–365.

Nishida Y, Hosomi S, Yamagami H, Yukawa T, Otani K, Nagami Y, Tanaka F, Taira K, Kamata N, Tanigawa T & Shiba M. (2017) Neutrophil-to-lymphocyte ratio for predicting loss of response to infliximab in ulcerative colitis. *PLoS ONE* 12, e0169845.

Peyton CC, Colaco MA, Kovell RC, Kim JH & Terlecki RP. (2016) Erectile dysfunction is predictive of endothelial dysfunction in a well visit population. *J Urol* 195, 1045–1050.

Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J & Mishra A. (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 49, 822–830.

Salonia A, Castagna G, Saccà A, Ferrari M, Capitanio U, Castiglione F, Rocchini L, Briganti A, Rigatti P & Montorsi F. (2012) Is erectile dysfunction a reliable proxy of general male health status? The case for the international index of erectile function-erectile function domain. *Journal of Sexual Medicine* 9, 2708–2715.

Sikka SC, Hellstrom WJ, Brock G & Morales AM. (2013) Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. *J Sex Med* 10, 120–129.

Vardi Y, Dayan L, Apple B, Gruenwald I, Ofer Y & Jacob G. (2009) Penile and systemic endothelial function in men with and without erectile dysfunction. *Eur Urol* 55, 979–985.

Vignozzi L, Morelli A, Sarchielli E, Comeglio P, Filippi S, Cellai I, Maneschi E, Serni S, Gacci M, Carini M & Piccinni MP. (2012) Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit. *J Endocrinol* 212, 71–84.

Vlachopoulos C, Aznaouridis K, Ioakeimidis N, Rokkas K, Vasiliadou C, Alexopoulos N, Stefanadi E, Askitis A & Stefanadis C. (2006) Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J* 27, 2640–2648.

Vlachopoulos C, Rokkas K, Ioakeimidis N & Stefanadis C. (2007) Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. *Eur Urol* 52, 1590–1600.

Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, Aznaouridis KA & Stefanadis CI. (2013) Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. *Circ Cardiovasc Qual Outcomes* 6, 99–109.

Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, Maggi M, Nelson CJ, Parish S, Salonia A & Tan R. (2016) Erectile dysfunction. *Nat Rev Dis Primers* 2, 16003.

Yamada T, Hara K, Umematsu H, Suzuki R & Kadowaki T. (2012) Erectile dysfunction and cardiovascular events in diabetic men: a meta-analysis of observational studies. *PLoS ONE* 7, e43673.

Zhang JH, Ferrante AN, Arrigo AP & Dayer JM. (1992) Neutrophil stimulation and priming by direct contact with activated human T lymphocytes. *J Immunol* 148, 177–181.

