Send Orders for Reprints to reprints@benthamscience.net

Endocrine, Metabolic & Immune Disorders-Drug Targets, **XXXX,** ***XX,*** **1-9**

RESEARCH ARTICLE

Erectile Dysfunction in Patients with Multiple Chronic Conditions: A Cross-Sectional Study

Giuseppe Lisco[1], Nicola Bartolomeo[2], Maria Isabella Ramunni[3], Anna De Tullio[1], Matteo Domenico Carbone[4], Edoardo Guastamcchia[1], Giovanni De Pergola[5], Vincenzo Triggiani[1] and Vito Angelo Giagulli[1,3,*]

[1]Section of Internal Medicine, Geriatrics, Endocrinology, and Rare Disease, Interdisciplinary Department of Medicine, University of Bari, School of Medicine, Policlinico, Bari, Italy; [2]Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy; [3]Outpatients Clinic of Endocrinology and Metabolic Disease, Conversano Hospital, Bari, Italy; [4]Institute of Clinical and Hormonal Research, Foggia, Italy; [5]Scientific Direction, Research Hospital, National Institute of Gastroenterology "Saverio de Bellis", Castellana Grotte, Bari, Italy

ARTICLE HISTORY

Received: November 11, 2021
Revised: March 29, 2022
Accepted: April 4, 2022

DOI:
10.2174/1871530322666220523130212

Abstract: ***Background*****:** The prevalence of erectile dysfunction (ED) rises with the number and severity of chronic diseases.

Aims**:** This cross-sectional study assessed the frequency and severity of ED in patients with multiple chronic conditions.

Methods**:** The 5-item International Index of Erectile Function questionnaire (IIEF-5) was used to diagnose and classify ED. The Charlson Comorbidity Index (CCI) was used to assess the burden of chronic comorbidity. The primary outcome was to assess the ED frequency according to CCI severity. The secondary outcomes included the assessment of the correlation between 1) IIEF-5 and total testosterone (TT), 2) CCI and TT, and 3) IIEF-5 and CCI. Lastly, the CCI and modified CCI (mCCI) performances were compared with each other.

Results**:** The overall frequency of ED increased along with the CCI score severity: 45% for CCI=0; 95% for CCI=1; 91% for CCI=2; 99% for CCI≥3 ($p<.0001$). CCI correlated negatively with TT levels and IIEF-5 score ($r=-0.34$ and -0.44; $p<.0001$). Compared to the CCI, a novel proposed mCCI performs well.

Discussion**:** The frequency and severity of ED are relevant in outpatients with sexual complaints and those with chronic comorbidities. Despite limitations, mCCI may be considered a reliable tool to assess the overall burden of multiple chronic conditions in patients with comorbidities.

Conclusion**:** ED is a reliable proxy of overall male health. Further studies are needed to confirm this potential application.

Keywords: Erectile dysfunction, Charlson comorbidity index, type 2 diabetes, comorbidities, cross-sectional study.

1. INTRODUCTION

Erectile dysfunction (ED) is a sexual disorder characterized by the inability to attain and maintain penis erection for obtaining satisfactory sexual intercourse [1]. It is an independent risk factor for poor health, reduced quality of life, and decreased survival. For instance, ED increases the risk of future cardiovascular events, including myocardial infarction, cerebrovascular events, and all-cause mortality [2-4]. Screening men with ED for cardiovascular disease and treating them for both disorders are cost-effective [5].

*Address correspondence to this author at the Outpatients Clinic of Endocrinology and Metabolic Disease, Conversano Hospital, Bari, Italy;
Tel: +39 (0) 80 409 13 68; E-mail: vitogiagulli58@gmail.com

The estimated prevalence of ED increases along with aging. ED affects mainly men over 40 years old, with a prevalence ranging from 2% to 9% in those aged 40-49 years and 50% to 100% in those older than 70 years [6]. Two main mechanisms explain this phenomenon. First, erectile performance is related to serum total testosterone (TT) levels, and an age-related decline in TT concentrations is known to occur, as observed in the European Male Aging Study [7, 8]. Testosterone is a strong determinant of sex drive in men and plays a role in maintaining the homeostasis and morphology of corpus cavernosum components and nitric oxide production [9, 10]. Second, the burden of chronic diseases increases with aging and is independently associated with ED [7,11]. Lifestyle

1389-2010/XX $65.00+.00

modifications [12], pharmacotherapy [13], and other interventions such as bariatric surgery [14] usually improve sexual function.

The Charlson Comorbidity Index (CCI) is a validated and simple-to-use tool to classify chronic comorbidities and predict ten-year mortality. Compared to other indexes, CCI considers both the number and severity of 19 pre-defined conditions, assigning each of them a specific weight [15, 16].

The present cross-sectional study was conceived to investigate the impact of weighted chronic comorbidities on both the frequency and severity of ED. Notably, we aimed to evaluate the association between the burden of comorbidities assessed by a widely used and validated method (CCI) and the frequency and severity of ED. In this order, we retrospectively analyzed adult men who were evaluated at our institution for ED complaints.

2. MATERIALS AND METHODS

2.1. Institutional Management of Men with ED Complaints

This study was carried out in a secondary referral center for endocrine diseases and metabolic disorders accredited by the Italian Society of Andrology and Sexual Medicine (SIAMS), the Outpatients Clinic of Endocrinology, and Metabolic Disease of Conversano Hospital (Italy).

In individuals complaining of ED, the initial evaluation included: 1) collection of detailed medical and sexual history, 2) physical examination and anthropometry, including blood pressure, body weight, height, body mass index (BMI) calculation, and waist circumference (WC), 3) laboratory testing including fasting plasma glucose, HbA_{1c}, lipid profile, and measurement of serum androgens and gonadotropins (LH, FSH), and 4) questionnaires (*i.e.*, IIEF-5). TT, LH, and FSH were measured in all patients. In men with medical conditions affecting the levels of sex hormone-binding globulin (SHBG) or whose initial TT concentrations were at or near the lower limit of the normal range (*e.g.*, 300 ng/dL [10.4 nM/L]), SHBG was also measured [17]. ED was diagnosed and classified according to the 5-item International Index of Erectile Function questionnaire (IIEF-5) [18]. Additional procedures were performed when indicated. Given the high prevalence of cardiovascular disease, a multidisciplinary diagnostic workup was considered. Other laboratory measurements (*e.g.*, PSA, prolactin) and further investigations (*e.g.*, a workup for obstructive sleep apnea) were assessed in subjects with specific signs and associated symptoms. Different procedures (multiple pituitary hormone assessments, genetic analysis, magnetic resonance imaging) were carried out in men with serum TT <150 ng/dL (5.2 nM/L) to rule out the organic form of hypogonadism [19-21]. CCI score was also calculated to assess the burden of multiple chronic conditions. Additionally, as common risk factors for ED (*e.g.*, arterial hypertension, dyslipidemia, and cigarette smoke) are not included in the classical CCI, we developed a modified index (mCCI).

2.2. Study Design

This was a cross-sectional study. The study period was from January 1, 2018, to December 31, 2019. All consecutive men complaining of ED for whom serum TT, IIEF-5 questionnaire, and a complete anamnestic collection were available were searched in the institutional database and considered eligible for the study. All procedures were carried out according to the University of Bari (protocol number 6454, July 2020) and the Azienda Sanitaria Locale (protocol number: 1294, October 2020) ethical standard, following the Declaration of Helsinki. Only patients who signed informed consent to treat personal data for clinical research purposes were included.

2.3. Inclusion Criteria

Patients were considered eligible for the study according to the following criteria: age >18 years; ED complaints; signature of informed consent to treat personal data for clinical research purposes.

2.4. Exclusion Criteria

Patients were excluded if any relevant data were missed, incomplete, or useless, including IIEF-5 and CCI scores and in the case of not meeting diagnostic criteria for ED. The flow diagram of patient selection is shown in Fig. (**1**).

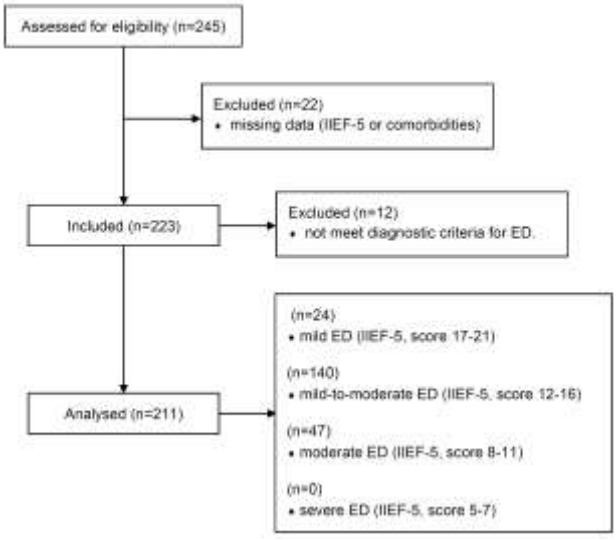

Fig. (1). Flow diagram of patients selection.

2.5. Procedures

Each patient completed the IIEF-5 questionnaire. ED was defined as an IIEF-5 score ≤21 and was classified as severe for scores 5-7, moderate for scores 8-11, mild to moderate for scores 12-16, and mild for scores 17-21 [18]. Self-reported or newly diagnosed comorbidities were used to calculate the CCI score. Clinical conditions and associated scores were as follows:

- cerebrovascular disease, chronic lung disease, heart failure, connective tissue diseases, dementia, diabetes mellitus, mild liver disease, myocardial infarction, peripheral vascular disease, and foot ulcers were assigned 1 point;
- any tumor, diabetes with end-organ damage, hemiplegia, leukemia, lymphoma, and moderate or severe kidney disease (eGFR <60 ml/min) were assigned 2 points;
- moderate or severe liver diseases were assigned 3 points;

- acquired immunodeficiency syndrome (AIDS) and solid metastatic tumor were assigned 6 points [15].

Additional risk factors for ED that were not initially included in the CCI were considered in our mCCI, and 1 point was additionally added for each of the following conditions: arterial hypertension, dyslipidemia, and cigarette smoke [4, 22].

2.6. Laboratory Measurements

Hormonal parameters were exclusively measured in the central hospital laboratory as for usual clinical practice. Each blood specimen was collected between 8 and 9 am after an overnight fast and stored at -20°C until analyzed. Serum LH, FSH, TT, and SHBG were measured by commercial immunometric assays (Immulite, EURO/DPC, UK). Reference range were 7.5 ± 2.6 IU/L for LH, 6.6 ± 2.5 IU/L for FSH, 450 ± 90 ng/dL for TT (15.6±3.1 nM/L) and 45.4 ± 5.1 nM/L for SHBG. Intra- and inter-assay coefficients of variation of these methods were <8% and <10%, respectively [17].

2.7. Statistical Analysis

All analyses were carried out using SAS 9.4 software (SAS Institute, Cary, NC, USA).

The primary outcome was to assess the frequency of ED according to the level of severity of CCI. The secondary outcomes included the correlation between 1) IIEF-5 and TT; 2) CCI and TT; 3) IIEF-5 and CCI. Lastly, the performance of the CCI and mCCI were compared with each other. Continuous variables were expressed as mean and standard deviation (SD) for normally distributed parameters or the median and interquartile range (IQR) in skewed data distribution. Shapiro-Wilk's statistics were used to test normality, and an appropriate function was applied to transform those showing a non-normal distribution. The distribution of patients in each category was described as frequency and proportion. Chi-square test and Chi-squared test for trend were used to verify the association between ED and CCI grouped in four classes (score = 0, score = 1, score = 2, score ≥ 3). Pearson's correlation coefficient or Spearman's non-parametric correlation coefficient was used to test the secondary outcomes, as necessary, and the Mardia test was used to verify multivariate normality. Univariate and multivariable linear models were applied to evaluate the effect of the parameters age, BMI, TT, LH, FSH, SHBG, albumin, and CCI on the IIEF-5 scores. The R-squared value and the residual normality test were used to evaluate the goodness of fit of the multivariable model. All tests of statistical significance were two-tailed, and p-values less than 0.05 were considered statistically significant.

3. RESULTS

Two-hundred forty-five men were eligible according to the study purpose. Twenty-two participants were excluded because of missing data related to the IIEF-5 questionnaire or comorbidities. Other twelve men were excluded as they did not meet the criteria for ED. Therefore, 211 men aged 18 to 92 years were analyzed: 181 (86%) had type 2 diabetes; 182 (86%) had arterial hypertension; 192 (91%) were on statins, and 94 (44%) were current smokers. Medications for treating diabetes mellitus were prescribed as follows: 75% were on metformin; 30% on GLP-1 receptor agonists; 25% on sodium-glucose cotransporter 2 inhibitors; 5% were on basal insulin therapy. Among hypertensive men, 73% were on angiotensin-converting enzyme inhibitors, 14% on angiotensin receptor antagonists, 41% on calcium channel blockers, 8% on β-blockers, and 9 % on diuretics. None were assuming specific treatment for ED or other sexual and reproductive disorders. Based upon the results of the IIEF-5 questionnaire, ED was classified as mild in 24 men (11%), mild-to-moderate in 140 (66%), and moderate in 47 (23%) (Table **1**).

The overall frequency of ED increased along with the CCI score: 45% (5 on 11) for CCI=0; 95% (19 on 20) for CCI=1; 91% (29 on 32) for CCI=2; 99% (158 on 160) for CCI≥3 (p<.0001) (Fig. **2**). A direct correlation between the IIEF-5 score and TT levels was found, as expected (r=0.67; p<.0001) (Fig. **3**). Moreover, CCI correlated with both serum TT levels and IIEF-5 scores, meaning that a higher burden of weighted comorbidities was inversely correlated to lower serum testosterone levels and worse erectile function (r=-0.34 and -0.44; p<.0001, respectively) (Figs. **4** and **5**). Table **2** shows the results of the univariate and multivariate analyses on parameters associated with the IIEF-5 score. A lower IIEF-5 score was significantly and independently associated with higher age and CCI as well as lower TT and SHBG. The R-squared of the model was 0.65. The residuals were normally distributed according to Shapiro-Wilk's test, as expected in a goodness of fit.

Since arterial hypertension, dyslipidemia, and cigarette smoking were not included in the original CCI score, we developed an mCCI. As found for the CCI, the overall frequency of ED in the four classes of the mCCI differed as follows: 0% (0 on 1) for mCCI=0; 57% (4 on 7) for mCCI=1; 73% (8 on 11) for mCCI=2; 98% (199 on 204) for mCCI≥3 (p<.0001). The correlation between the mCCI, TT, and IIEF-5 scores was confirmed. Compared to the CCI, an equal performance was found.

4. DISCUSSION

ED is a common sexual disorder in elderly men. The prevalence of comorbidities increases with age, and multiple chronic conditions are known to be associated with ED [23]. We carried out this study to specifically evaluate the performance of one of the most validated comorbidities indexes (CCI) in diagnosing ED and classifying its severity. The IIEF-5 questionnaire assessed the presence and severity of ED in men referred to our institution due to ED complaints. The burden of comorbidities was estimated by the CCI and a mCCI that included other variables not originally contemplated in the CCI, such as arterial hypertension, dyslipidemia, and cigarette smoke. Less than 10% of participants with ED were on diuretics and beta-blockers that may affect erectile function [24].

The main result of the present study showed that CCI is a reliable tool for assessing the presence and severity of ED. The overall ED prevalence (IIEF≤21) increases from 45% in men without comorbidities (CCI=0) to 99% in those whose CCI was equal or greater than 3. Additionally, although no patients with severe ED were retrieved, the severity of ED increased along with the burden of chronic comorbidities.

Table 1. Characteristics of included men.

-		**Analyzed (n=221)**
Age, years ± sd		60.8 ± 11.4
Bodyweight, kg [CI]		89.0 [78.3-100.8]
Body mass index, kg/m^2 [CI]		31.9 [27.0-34.5]
Total testosterone, ng/dL ± sd		313.2 ± 64.2
LH, IU/L ± sd		6.6 ± 2.5
FSH, IU/L ± sd		8.3 ± 5.2
SHBG, nM/L ± sd		38.2 ± 7.7
IIEF-5, score [CI]		14 [12-16]
Comorbidities included in the Charlson Comorbidity Index, number of individuals (%)		-
1 point	Cerebrovascular disease	24 (10.8%)
	Chronic lung disease	52 (23.5%)
	Heart failure	28 (12.7%)
	Connective tissue disease	12 (5.4%)
	Dementia	5 (2.2%)
	Diabetes without end-organ damage	76 (34.4%)
	Mild liver disease	110 (49.8%)
	Myocardial infarction	46 (20.8%)
	Peripheral vascular disease	30 (13.6%)
	Ulcer	26 (11.7%)
2 points	Any tumor	35 (15.8%)
	Diabetes with end-organ damage	105 (47.5%)
	Hemiplegia	1 (0.4%)
	Leukemia	4 (1.8%)
	Lymphoma	2 (0.9%)
	Moderate or severe kidney disease	46 (20.8%)
3 points	Moderate or severe liver disease	8 (3.6%)
6 points	AIDS	0 (0.0%)
	Metastatic solid tumor	5 (2.3%)
Other data, number of individuals (%)		-
Arterial hypertension		182 (82.3%)
Dyslipidemia		192 (86.9%)
Current cigarette smokers		94 (42.5%)

Abbreviations: sd=standard deviation; CI=confidence interval.

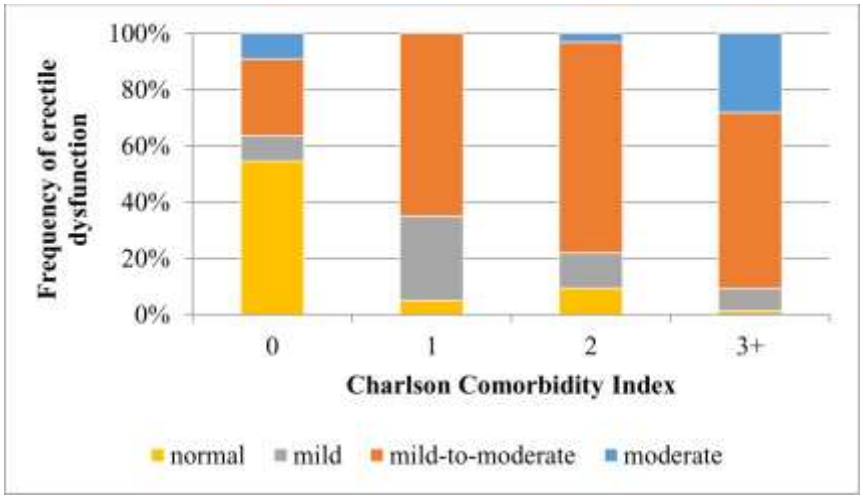

Fig. (2). Frequency of erectile dysfunction according to the Charlson Comorbidity index. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

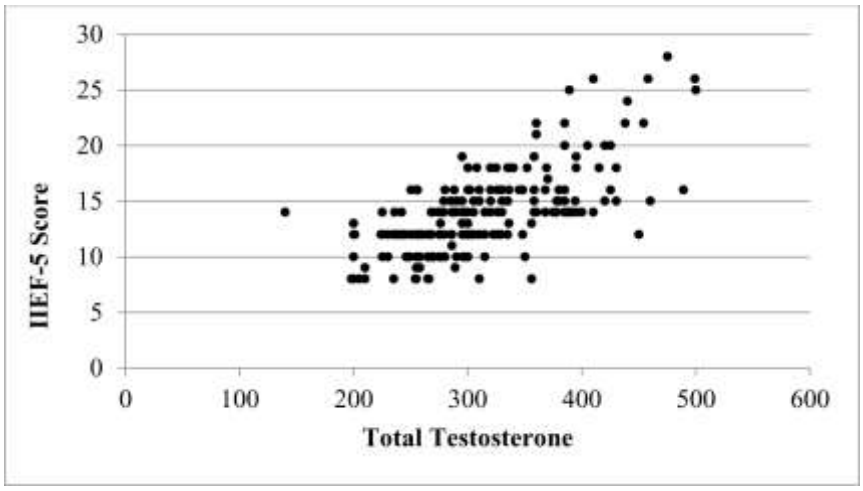

Fig. (3). Correlation between IIEF-5 and total testosterone. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

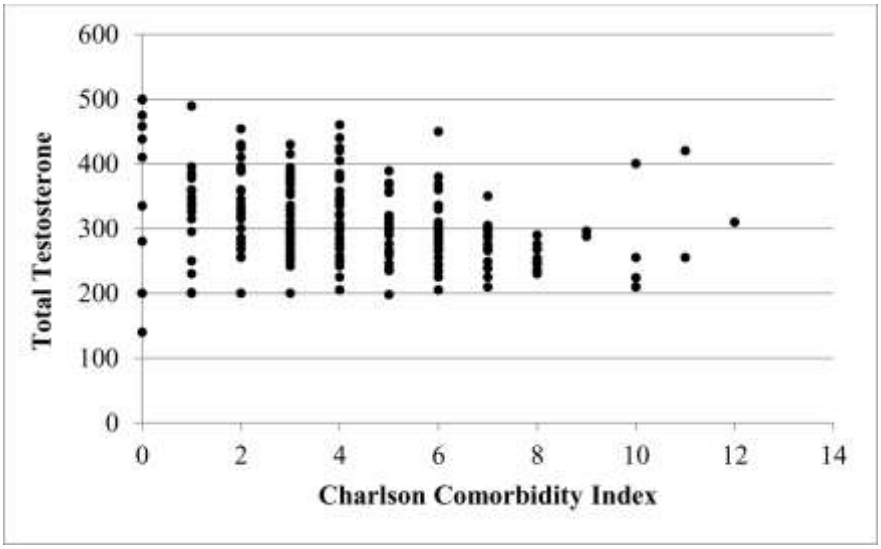

Fig. (4). Correlation between Charlson Comorbidity index and total testosterone. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

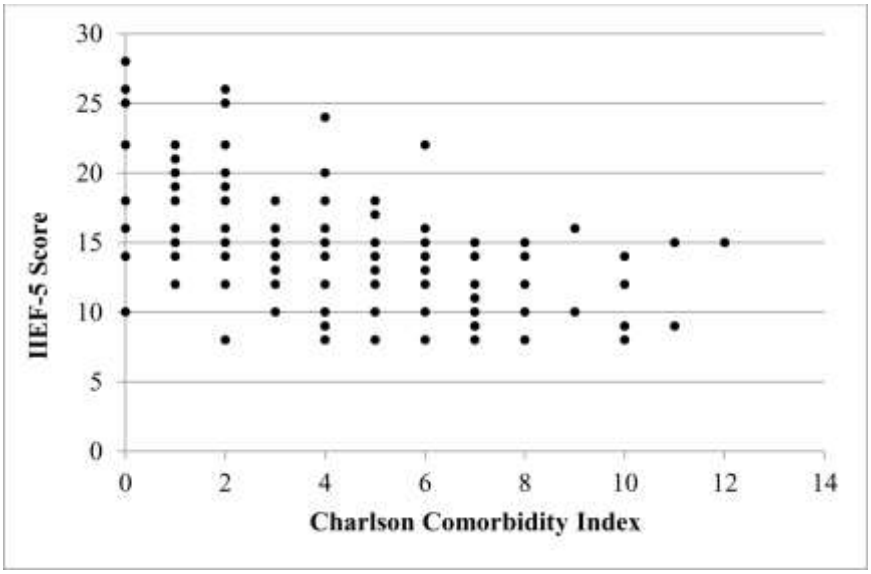

Fig. (5). Correlation between Charlson Comorbidity Index and IIEF-5 score. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 2. Factors associated with IIEF-5 score.

Parameters	Univariate		Multivariate	
	Effect (±se)	p-value	Effect (±se)	p-value
Age	-0.10±0.02	<.0001	-0.06±0.02	0.0004
Body mass index	-0.28±0.04	<.0001	-0.05±0.03	0.1115
Total testosterone	0.04±0.003	<.0001	0.03±0.003	<.0001
LH	-0.005±0.06	0.9316	-	-
FSH	-0.007±0.05	0.8829	-	-
SHBG	0.22±0.03	<.0001	0.10±0.03	0.0001
Albumina	-0.05±0.10	0.6233	-	-
Charlson Comorbidity Index score	-0.71±0.10	<.0001	-0.28±0.08	0.0005

Abbreviations: se=standard error.

The following correlations supported the reliability of these data. As expected, men with lower IIEF-5 scores had lower TT. Lower IIEF-5 scores and serum TT levels were found in patients with higher CCI, as well. The reliability of the mCCI was confirmed, although no improved performance was found compared to the standard CCI.

Two practical implications may follow. First, men complaining of ED are prone to receive a diagnosis of ED with any severity, even when single comorbidity is present at the time of the first diagnosis. This possibility is close to 100% in those men with moderate or severe liver disease or solid metastatic tumor as well as in those men with a combination of multiple chronic conditions scores at least 3 points (*e.g*., diabetes mellitus, heart failure, and non-alcoholic fatty liver disease; diabetes mellitus and renal insufficiency; diabetes mellitus, arterial hypertension, and cigarette smoke). Second, the burden of comorbidities assessed by CCI (and mCCI) can be used as a reliable proxy for ED. Several studies evaluating the performance of CCI in men with ED have been published. In 2012, Salonia *et al*. included 140 men who underwent dynamic penile color-doppler ultrasonography for new-onset ED in the University Vita-Salute San Raffaele [25]. In 2017, Favilla *et al*. included 425 sexually active men seeking a prostate health screening with table sexual relationship and normal testosterone levels in the Department of Urology of the University of Catania [26]. In 2018, Garcia-Cruz *et al*. included 430 men referred to seven urological units in Spain [27]. All these studies concluded that CCI could be a reliable tool to assess overall male sexual health. Our study extends the current knowledge about this topic based on data from patients referred to an endocrine diseases and metabolic disorders center, thus exhibiting different clinical characteristics, especially due to an elevated frequency of type 2 diabetes (in our cohort was 81%) compared to that reported in the cited studies (around 20%). Type 2 diabetes is a well-recognized risk factor for ED [28]. Hyperglycemia per se and chronic diabetes-related complications (*i.e*., microvascular) and comorbidities

(*i.e.*, obesity and cardiovascular diseases) are strictly implicated in the pathophysiology of ED [29]. The severity of ED is related to cardiovascular risk, and patients with severe and possibly moderate ED should be considered at higher risk of all-cause mortality in the general population [30]. A piece of evidence suggests that at least one-third of patients with ED fail to respond to symptomatic therapy (*i.e.*, phosphodiesterase-5 inhibitors), and this burden is even more revenant in men with diabetes. This is attributable, at least in part, to the fact that ED has a multifactorial etiology, including neurovascular, hormonal, and psychological factors. Prompt recognition and understanding of the leading cause(s) of complaints of ED are expected to improve the management of men who will be diagnosed with ED. On the other side, prompt recognition of ED should be considered an early warning sign of cardiovascular risk, especially in young men and in those with severe ED, and may improve the long-term prognosis of these patients [31].

The strengths and limitations of the present paper should also be discussed. First, a significant number of men was included in the present study, but this number can be considered relatively small compared to the burden of ED in the general population. Secondly, this was a single-center study in which all procedures were consistently carried out by the same medical team during the observation. Third, CCI evaluates the weight of chronic comorbid conditions, and it is well known that a different delay in diagnosis exists for some of them, including diabetes [32] and arterial hypertension [33]. An underestimation of CCI can be anticipated. To avoid this matter, we included both self-reported and documented diagnoses at the time of the initial assessment. Lastly, when the mCCI was conceived, the authors gave the same weight to the three "novel" variables and arbitrarily established 1 point for each one. Despite the role of hypertension, dyslipidemia, and cigarette smoke in the pathogenesis of ED, the burden of these comorbidities could not be the same and could also be affected by medical treatment and achieved therapeutic targets [34, 35].

CONCLUSION

The ED prevalence is known to increase with aging, and the same holds for the number of chronic conditions. The present study found that CCI, a validated tool to assess the burden of chronic comorbidities, positively correlates with the frequency and severity of ED. On the one hand, this confirms that ED is a reliable proxy of overall male health. On the other hand, this implies that a systematic ED assessment among individuals with chronic comorbidities could lead to a significant increase in the number of ED diagnoses, with a more severe ED being diagnosed in men with a higher burden of comorbidities. From a population study perspective, our data provide the rationale to assess the diagnostic performance of CCI (and mCCI) as a proxy for ED. However, further studies are needed to confirm this potential application.

LIST OF ABBREVIATIONS

AIDS	=	Acquired immunodeficiency syndrome
BMI	=	Body mass index
CCI	=	Charlson comorbidity index
ED	=	Erectile dysfunction
IIEF-5	=	International index of erectile function questionnaire
WC	=	Waist circumference

AUTHORS' CONTRIBUTIONS

V.A.G. conceived the study. V.A.G., G.L., and V.T. drafted the manuscript. N.B. provided statistical expertise. All the authors read, provided feedback, and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the University of Bari (protocol number 6454, July 2020) and the Azienda Sanitaria Locale (protocol number: 1294, October 2020) ethical standard.

HUMAN AND ANIMAL RIGHTS

All procedures were carried out according to the University of Bari (protocol number 6454, July 2020) and the Azienda Sanitaria Locale (protocol number: 1294, October 2020) ethical standard, following the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Only patients who signed informed consent to treat personal data for clinical research purposes were included.

STANDARD OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

CONFLICT OF INTEREST

Dr. Vincenzo Triggiani is the Associate Editor of the journal Endocrine, Metabolic & Immune Disorders-Drug Targets.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA*, **1993**, *270*(1), 83-90. http://dx.doi.org/10.1001/jama.1993.03510010089036 PMID: 8510302

[2] Dong, J.Y.; Zhang, Y.H.; Qin, L.Q. Erectile dysfunction and risk of cardiovascular disease: Meta-analysis of prospective cohort studies. *J. Am. Coll. Cardiol.*, **2011**, *58*(13), 1378-1385.

http://dx.doi.org/10.1016/j.jacc.2011.06.024 PMID: 21920268

[3] Zhao, B.; Hong, Z.; Wei, Y.; Yu, D.; Xu, J.; Zhang, W. Erectile dysfunction predicts cardiovascular events as an independent risk factor: A systematic review and meta-analysis. *J. Sex. Med.*, **2019**, *16*(7), 1005-1017.

http://dx.doi.org/10.1016/j.jsxm.2019.04.004 PMID: 31104857

[4] Burnett, A.L.; Nehra, A.; Breau, R.H.; Culkin, D.J.; Faraday, M.M.; Hakim, L.S.; Heidelbaugh, J.; Khera, M.; McVary, K.T.; Miner, M.M.; Nelson, C.J.; Sadeghi-Nejad, H.; Seftel, A.D.; Shindel, A.W. Erectile dysfunction: AUA guideline. *J. Urol.*, **2018**, *200*(3), 633-641.

http://dx.doi.org/10.1016/j.juro.2018.05.004 PMID: 29746858

[5] Giagulli, V.A.; Moghetti, P.; Kaufman, J.M.; Guastamacchia, E.; Iacoviello, M.; Triggiani, V. Managing erectile dysfunction in heart failure. *Endocr. Metab. Immune Disord. Drug Targets*, **2013**, *13*(1), 125-134.

http://dx.doi.org/10.2174/1871530311313010015 PMID: 23369145

[6] Shamloul, R.; Ghanem, H. Erectile dysfunction. *Lancet*, **2013**, *381*(9861), 153-165.

http://dx.doi.org/10.1016/S0140-6736(12)60520-0 PMID: 23040455

[7] Wu, F.C.; Tajar, A.; Pye, S.R.; Silman, A.J.; Finn, J.D.; O'Neill, T.W.; Bartfai, G.; Casanueva, F.; Forti, G.; Giwercman, A.; Huhtaniemi, I.T.; Kula, K.; Punab, M.; Boonen, S.; Vanderschueren, D. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: The European Male Aging Study. *J. Clin. Endocrinol. Metab.*, **2008**, *93*(7), 2737-2745.

http://dx.doi.org/10.1210/jc.2007-1972 PMID: 18270261

[8] Wu, F.C.; Tajar, A.; Beynon, J.M.; Pye, S.R.; Silman, A.J.; Finn, J.D.; O'Neill, T.W.; Bartfai, G.; Casanueva, F.F.; Forti, G.; Giwercman, A.; Han, T.S.; Kula, K.; Lean, M.E.; Pendleton, N.; Punab, M.; Boonen, S.; Vanderschueren, D.; Labrie, F.; Huhtaniemi, I.T. Identification of late-onset hypogonadism in middle-aged and elderly men. *N. Engl. J. Med.*, **2010**, *363*(2), 123-135.

http://dx.doi.org/10.1056/NEJMoa0911101 PMID: 20554979

[9] Rajfer, J. Relationship between testosterone and erectile dysfunction. *Rev. Urol.*, **2000**, *2*(2), 122-128.

PMID: 16985751

[10] Castela, A.; Vendeira, P.; Costa, C. Testosterone, endothelial health, and erectile function. *ISRN Endocrinol.*, **2011**, *2011*, 839149.

http://dx.doi.org/10.5402/2011/839149 PMID: 22363891

[11] Rastrelli, G.; Corona, G.; Maggi, M. Both comorbidity burden and low testosterone can explain symptoms and signs of testosterone deficiency in men consulting for sexual dysfunction. *Asian J. Androl.*, **2020**, *22*(3), 265-273.

http://dx.doi.org/10.4103/aja.aja_61_19 PMID: 31249270

[12] Silva, A.B.; Sousa, N.; Azevedo, L.F.; Martins, C. Physical activity and exercise for erectile dysfunction: Systematic review and meta-analysis. *Br. J. Sports Med.*, **2017**, *51*(19), 1419-1424.

http://dx.doi.org/10.1136/bjsports-2016-096418 PMID: 27707739

[13] Cai, X.; Tian, Y.; Wu, T.; Cao, C.X.; Bu, S.Y.; Wang, K.J. The role of statins in erectile dysfunction: A systematic review and meta-analysis. *Asian J. Androl.*, **2014**, *16*(3), 461-466.

http://dx.doi.org/10.4103/1008-682X.123678 PMID: 24556747

[14] Glina, F.P.A.; de Freitas Barboza, J.W.; Nunes, V.M.; Glina, S.; Bernardo, W.M. What is the impact of bariatric surgery on erectile function? A systematic review and meta-analysis. *Sex. Med. Rev.*, **2017**, *5*(3), 393-402.

http://dx.doi.org/10.1016/j.sxmr.2017.03.008 PMID: 28526630

[15] Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.*, **1987**, *40*(5), 373-383.

http://dx.doi.org/10.1016/0021-9681(87)90171-8 PMID: 3558716

[16] Austin, S.R.; Wong, Y.N.; Uzzo, R.G.; Beck, J.R.; Egleston, B.L. Why summary comorbidity measures such as the Charlson comorbidity index and Elixhauser score work. *Med. Care*, **2015**, *53*(9), e65-e72.

http://dx.doi.org/10.1097/MLR.0b013e318297429c PMID: 23703645

[17] Vermeulen, A.; Verdonck, L.; Kaufman, J.M. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J. Clin. Endocrinol. Metab.*, **1999**, *84*(10), 3666-3672.

http://dx.doi.org/10.1210/jcem.84.10.6079 PMID: 10523012

[18] Rosen, R.C.; Cappelleri, J.C.; Smith, M.D.; Lipsky, J.; Peña, B.M. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int. J. Impot. Res.*, **1999**, *11*(6), 319-326.

http://dx.doi.org/10.1038/sj.ijir.3900472 PMID: 10637462

[19] Bhasin, S.; Brito, J.P.; Cunningham, G.R.; Hayes, F.J.; Hodis, H.N.; Matsumoto, A.M.; Snyder, P.J.; Swerdloff, R.S.; Wu, F.C.; Yialamas, M.A. Testosterone therapy in men with hypogonadism: An endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.*, **2018**, *103*(5), 1715-1744.

http://dx.doi.org/10.1210/jc.2018-00229 PMID: 29562364

[20] Salonia, A.; Bettocchi, C.; Carvalho, J. EAU guidelines on Sexual and Reproductive Health. Available from: https://uroweb.org/guideline/sexual-and-reproductive-health/

[21] Giagulli, V.A.; Castellana, M.; Carbone, M.D.; Pelusi, C.; Ramunni, M.I.; De Pergola, G.; Guastamacchia, E.; Triggiani, V. Weight loss more than glycemic control may improve testosterone in obese type 2 diabetes mellitus men with hypogonadism. *Andrology*, **2020**, *8*(3), 654-662.

http://dx.doi.org/10.1111/andr.12754 PMID: 31919991

[22] Giagulli, V.A.; Carbone, M.D.; Ramunni, M.I.; Licchelli, B.; De Pergola, G.; Sabbà, C.; Guastamacchia, E.; Triggiani, V. Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism. *Andrology*, **2015**, *3*(6), 1094-1103.

http://dx.doi.org/10.1111/andr.12099 PMID: 26447645

[23] Hackett, G. The burden and extent of comorbid conditions in patients with erectile dysfunction. *Int. J. Clin. Pract.*, **2009**, *63*(8), 1205-1213.

http://dx.doi.org/10.1111/j.1742-1241.2009.02088.x PMID: 19624788

[24] Chrysant, S.G. Antihypertensive therapy causes erectile dysfunction. *Curr. Opin. Cardiol.*, **2015**, *30*(4), 383-390.

http://dx.doi.org/10.1097/HCO.0000000000000189 PMID: 26049386

[25] Salonia, A.; Castagna, G.; Saccà, A.; Ferrari, M.; Capitanio, U.; Castiglione, F.; Rocchini, L.; Briganti, A.; Rigatti, P.; Montorsi, F. Is erectile dysfunction a reliable proxy of general male health status? The case for the International Index of Erectile Function-Erectile Function domain. *J. Sex. Med.*, **2012**, *9*(10), 2708-2715.

http://dx.doi.org/10.1111/j.1743-6109.2012.02869.x PMID: 22897643

[26] Favilla, V.; Russo, G.I.; Reale, G.; Leone, S.; Castelli, T.; La Vignera, S.; Condorelli, R.A.; Calogero, A.E.; Cimino, S.; Morgia, G. Predicting erectile dysfunction in sexually active patients seeking prostate health screening: Proposal for a multivariable risk stratification. *Int. J. Impot. Res.*, **2015**, *27*(6), 201-205.

http://dx.doi.org/10.1038/ijir.2015.15 PMID: 26224573

[27] García-Cruz, E.; Carrión, A.; Ajami, T.; Álvarez, M.; Correas, M.Á.; García, B.; García, J.V.; González, C.; Portillo, J.A.; Romero-Otero, J.; Simón, C.; Torremadé, J.; Vigués, F.; Alcaraz, A. The patient's comorbidity burden correlates with the erectile dysfunction severity. *Actas Urol. Esp.*, **2018**, *42*(1), 57-63.

http://dx.doi.org/10.1016/j.acuroe.2017.03.012 PMID: 28641871

[28] Kouidrat, Y.; Pizzol, D.; Cosco, T.; Thompson, T.; Carnaghi, M.; Bertoldo, A.; Solmi, M.; Stubbs, B.; Veronese, N. High prevalence of erectile dysfunction in diabetes: A systematic review and meta-analysis of 145 studies. *Diabet. Med.*, **2017**, *34*(9), 1185-1192.

http://dx.doi.org/10.1111/dme.13403 PMID: 28722225

[29] Mitidieri, E.; Cirino, G.; d'Emmanuele di Villa Bianca, R.; Sorrentino, R. Pharmacology and perspectives in erectile dysfunction in man. *Pharmacol. Ther.*, **2020**, *208*, 107493.

http://dx.doi.org/10.1016/j.pharmthera.2020.107493 PMID: 31991196

[30] Fan, Y.; Hu, B.; Man, C.; Cui, F. Erectile dysfunction and risk of cardiovascular and all-cause mortality in the general population: A meta-analysis of cohort studies. *World J. Urol.*, **2018**, *36*(10), 1681-1689.

http://dx.doi.org/10.1007/s00345-018-2318-3 PMID: 29725807

[31] Yannas, D.; Frizza, F.; Vignozzi, L.; Corona, G.; Maggi, M.; Rastrelli, G. Erectile dysfunction is a hallmark of cardiovascular disease: Unavoidable matter of fact or opportunity to improve men's health? *J. Clin. Med.*, **2021**, *10*(10), 2221.

http://dx.doi.org/10.3390/jcm10102221 PMID: 34065601

[32] Harris, M.I.; Klein, R.; Welborn, T.A.; Knuiman, M.W. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care*, **1992**, *15*(7), 815-819.

http://dx.doi.org/10.2337/diacare.15.7.815 PMID: 1516497

[33] Imam, H.; Sundström, J.; Lind, L. Evaluation of time delay between discovery of a high blood pressure in a health screening survey and hypertension diagnosis. *Blood Press.*, **2020**, *29*(6), 370-374.

http://dx.doi.org/10.1080/08037051.2020.1782726 PMID: 32603237

[34] Mirone, V.; Imbimbo, C.; Bortolotti, A.; Di Cintio, E.; Colli, E.; Landoni, M.; Lavezzari, M.; Parazzini, F. Cigarette smoking as risk factor for erectile dysfunction: Results from an Italian epidemiological study. *Eur. Urol.*, **2002**, *41*(3), 294-297.

http://dx.doi.org/10.1016/S0302-2838(02)00005-2 PMID: 12180231

[35] Selvin, E.; Burnett, A.L.; Platz, E.A. Prevalence and risk factors for erectile dysfunction in the US. *Am. J. Med.*, **2007**, *120*(2), 151-157.

http://dx.doi.org/10.1016/j.amjmed.2006.06.010 PMID: 17275456