# Multimorbidity and Disease Severity Measured by the Charlson Index in Portuguese Hospitalised Patients During the Year 2015: A Cross-Sectional Study

# Multimorbilidade e Gravidade da Doença Medida pelo Índice de Charlson em Doentes Hospitalizados Durante o Ano de 2015: Estudo Transversal

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## ABSTRACT

**Introduction:** The association between multimorbidity and disease severity is not well established. The objectives were to characterise multimorbidity and determine disease severity (trough Charlson), as well as to verify if there is an association between the number and type of disease and the Charlson index.

**Material and Methods:** A cross-sectional study based on exported data from the Portuguese National Health Service hospitalisations database, during the year 2015. The study included 22 chronic health conditions: 15 predicted in the Charlson index and seven frequent conditions (hypertension, obesity, dyslipidaemia, osteoarthritis, osteoporosis, anxiety and depression). The analysis was performed through the generalised linear model, considering binary logistic regression. In the analysis, the IBM SPSS version 24.0 tool was used.

**Results:** The study analysed 800 376 hospitalisations, from which 42% correspond to males. The average age of the sample was 59.8 years, being higher in men (62.3 years). The mean number of problems per person was 1.6, greater in men (1.8). Disease severity was also higher in males. The worst prognosis was associated with six or more conditions per person. The largest predictor of disease severity was the number of problems, followed by dementia and diabetes.

**Discussion:** The results seem to confirm the gender difference regarding morbidity pattern. The number of conditions per person was the greatest predictor of disease severity, particularly the presence of six or more conditions per person.

**Conclusion:** The major limitation was the use of the same medical conditions to measure multimorbidity and disease severity. Other studies and analysis models should explore the complexity of the multimorbidity phenomenon.


**Keywords:** Comorbidity; Multimorbidity; Portugal; Severity of Illness Index


## RESUMO

**Introdução:** A associação entre multimorbilidade e gravidade da doença não está bem estabelecida. Os objetivos foram caracterizar a multimorbilidade e determinar a gravidade da doença, bem como verificar se existe associação entre o número e natureza dos diagnósticos e o índice de Charlson.

**Material e Métodos:** Estudo transversal realizado através de dados exportados da base de dados de internamentos, durante o ano de 2015. O estudo incluiu 22 doenças crónicas: 15 previstas no índice de Charlson e sete condições médicas frequentes (hipertensão, obesidade, dislipidemia, osteoartrose, osteoporose, ansiedade e depressão). A análise foi realizada através do modelo linear generalizado, regressão logística binária. Na análise, utilizou-se a ferramenta IBM SPSS versão 24.0.

**Resultados:** Foram analisadas 800 376 hospitalizações, das quais 42% correspondem a homens. A idade média da amostra foi de 59,8 anos, sendo maior nos homens (62,3 anos). O número médio de problemas por pessoa foi de 1,6, sendo superior nos homens (1,8). A gravidade da doença também foi maior nos homens. O pior prognóstico esteve associado a seis ou mais condições por pessoa. O maior preditor de gravidade da doença foi o número de problemas, seguido da demência e diabetes.

**Discussão:** Os resultados parecem confirmar a diferença entre sexos quanto ao padrão de morbilidade. O número de condições por pessoa foi o maior preditor de gravidade da doença, particularmente a presença de seis ou mais condições por pessoa.

**Conclusão:** A principal limitação identificada foi o uso das mesmas condições médicas para medir a multimorbilidade e a gravidade da doença. Outros estudos e modelos de análise devem explorar a complexidade do fenómeno da multimorbilidade.


**Palavras-chave:** Comorbilidade; Índice de Gravidade de Doença; Multimorbilidade; Portugal

## INTRODUCTION

Multimorbidity and comorbidity refer to the 'co-occurrence of two or more medical conditions within a patient, additional to an index disease'.[1] Those defending the concept of multimorbidity tend to focus their attention on primary healthcare in which the identification of an index disorder may not always become obvious or useful.[1-4]

The estimated prevalence of multimorbidity is variable due to the lack of consensus on its definition, data collection and number of conditions considered.[4-10] The lack of standardisation leads to heterogeneous conclusions, making prevalence data not comparable.[4,7] As described, multimorbidity (MM) frequency is variable according to the length of

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the list of candidate conditions, ranging from 43.7% [(two or more conditions (MM2+)], 27.4% (MM3+), 14.7% (MM4+), 6.7% (MM5+) to 2.8% [six or more conditions (MM6+)].[9]

The fact that the estimated prevalence of multimorbidity is affected by the length of the list of candidate conditions is worth mentioning[4,6] as, for instance, when four to seven conditions were considered, an underestimated prevalence has been found, while a lower variability has been found when 12 or more conditions were used.[6] In addition, a low number of conditions (five) has led to a lower prevalence of multimorbidity (0.3% at the age of 32.5 and 3.5% at the age of 75), regardless of the sample size.[6]

In a Portuguese study, carried out in primary healthcare settings and involving adult population, nine out of 10 participants (87.0%) presented with at least one chronic condition, with a general average of 3.4 (3.6 in male, 3.3 in female patients).[11] Multimorbidity measured as MM2+ was presented by 72.7% of the patients, while a 57.2% rate was found when MM3+ was used.[11] A significant association ($p < 0.05$) has been found between multimorbidity and male gender, patient's age, living in rural areas, living alone, lower socioeconomic status (education and income),[11] in line with other studies showing an association between multimorbidity and poorer socioeconomic status.[11-13]

Interchangeability between both concepts has currently been found, even though the Charlson index is still used due to the fact that it gives a sense of severity to comorbidity alongside an index condition, defining the total burden of conditions with an impact on the patient.[1]

Different indices have been developed based on the number and severity of illness, leading to an aggregate score. Multimorbidity scores have been used in monitoring and in comparisons between groups of patients or healthcare providers.[14] The Charlson index was developed based on the relative risk of mortality and is used for the measurement of severity/intensity of illness, by using comorbidities with different impact on patient's outcome (e.g., weighting of six for metastatic solid tumour, two for diabetes with complications).[15,16] The Charlson index allows for the assessment of comorbidity (for instance, a score of three of more corresponds to severe comorbidity) and mortality prediction (e.g., score of five or more is predictive of death within three years, in 85% of the patients).[15] Good discrimination of short and long-term survival, predicting mortality with a high discriminant power has been found with the use of the Charlson index, both in primary and in secondary healthcare.[1718,19] With the advances in medicine and an increasing survival rate, conditions such as coronary artery disease, diabetes with no complications or cerebrovascular disease were not associated with mortality leading their weighting within the Charlson index to be questioned.[16] Nevertheless, it remains as a tool for the measurement of severity of illness, useful in the outcome assessment.[16,20]

The Charlson index has been widely used in studies of outcome assessment as it allows for valid comparisons and risk adjustment.[21,22] Risk adjustment is a complex construct involving patient's socio-demographic factors (patient's age, for instance), clinical stability or comorbidity severity and was developed as an indicator of the severity of illness.[13,22] An increasing interest has been found on the use of databases for morbidity assessment and the Charlson index applied to administrative data classified according to the ICD-9 system.[21-23] The Charlson index has been used for the assessment of the severity of illness in different epidemiological studies.[14,18-19,24] Administrative databases are used in epidemiological research in order to provide for supplementary information to primary studies as these correspond to real-life data, representing large groups of patients, with no selection bias.[21]

Considering the validity of the Charlson index as an outcome instrument for the assessment of the severity of illness,[20] the knowledge on whether or not an association between multimorbidity and severity of illness is crucial, considering conditions and age groups.

This study was aimed at the characterisation of multimorbidity in hospitalised patients admitted to public hospitals and the assessment of the severity of illness throughout the transition from early to late adulthood with the use of the Charlson index, as well as analysing any association between the index and the length of the list of candidate conditions and their nature.

## MATERIAL AND METHODS

This was a cross-sectional and descriptive study with an analytical component of data exported from the Portuguese national clinical *Grupos de Diagnósticos Homogéneos* (GDH) database.

The GDH database is a classification system of patients admitted to acute care hospitals according to clinically coherent groups of patients and with similar resource consumption profiles. These allow for the operative definition of which hospital products are provided to each patient according to patient's demands and the patient's pathology in which admission was based on, corresponding to the identification of conditions by hospital admission episode and by patient.

Only adult patients (aged 18 or over) admitted at least once to a public hospital throughout 2015 were included as study population.

The Charlson index was applied to ICD-9-CM administrative data obtained from the GDH database, allowing for the assessment of the severity of illness, in line with different other studies.[16,21-23] The Charlson index was obtained [23] according to the following steps: the ICD-10 codes that were assigned to each condition[25] were converted into ICD-9 codes and subsequently automatically weighted according to the score assigned to each condition (Table 1).

A pre-determined 15-item list of candidate conditions within the Charlson index was used for the assessment of the severity of illness, in which diabetes mellitus and liver disease had two different levels of severity, to which the most prevalent problems were added (hypertension, obesity, dyslipidaemia, osteoarthritis, osteoporosis, anxiety and depression)[11,16] leading to a total of 22 conditions (Table 1).

Table 1 – Conditions and ICD-9 coding correspondence

| Condition | Weighting | CID9 |
|---|---|---|
| Coronary artery disease | 1 | 410 410.00 410.01 410.02 410.10 410.11 410.12 410.2 410.20 410.21 410.22 410.3 410.30 410.31 410.32 410.4 410.40 410.41 410.42 410.5 410.50 410.51 410.52 410.6 410.60 410.61 410.62 410.7 410.70 410.72 410.8 410.80 410.82 410.9 410.90 410.91 410.92 |
| Congestive heart failure | 1 | 428 428.0 428.1 428.2 428.20 428.21 428.22 428.23 428.3 428.30 428.31 428.32 428.33 428.4 428.40 428.42 428.43 428.9 |
| Peripheral vascular disease | 1 | 440 440.0 440.1 440.2 440.20 440.21 440.22 440.3 440.30 440.31 440.32 440.4 440.8 440.9 441 441.0 441.00 441.01 441.02 441.3 441.1 441.2 441.4 441.5 441.6 441.7 441.9 442 442.0 442.1 442.2 442.3 442.8 442.81 442.82 442.83 442.84 442.89 442.9 443 443.0 443.1 443.2 443.21 443.22 443.23 443.24 443.29 443.8 443.81 443.82 443.89 443.9 |
| Cerebrovascular disease | 1 | 430 431 432 432.0 432.1 432.9 434 434.0 434.00 434.01 434.1 434.10 434.11 434.9 434.90 434.91 435 435.0 435.1 435.2 435.3 435.8 435.9 436 437 437.0 437.1 437.2 437.3 437.4 437.5 437.6 437.7 437.8 437.9 |
| Dementia | 1 | 290 290.0 290.1 290.10 290.11 290.12 290.13 290.2 290.20 290.21 290.3 290.4 290.40 290.41 290.42 290.43 290.8 290.9 291.2 292.82 294 294.1 294.10 294.11 294.2 294.20 294.21 |
| Connective tissue disease | 1 | 490 491 491.0 491.1 491.2 491.20 491.21 491.22 491.8 491.9 492 492.0 492.8 |
| Conectivite ou doença do conjuntivo | 1 | 517.2 695.4 710 710.0 710.1 710.2 710.3 710.4 710.5 710.8 710.9 714 714.0 714.1 714.2 714.3 714.30 714.31 714.32 714.33 714.4 714.8 714.81 714.89 714.9 725 |
| Peptic ulcer | 1 | 531 531.0 531.00 531.01 531.1 531.10 531.11 531.2 531.20 531.21 531.3 531.30 531.31 531.4 531.40 531.41 531.5 531.50 531.51 531.6 531.60 531.61 531.7 531.70 531.71 531.9 531.90 531.91 532 532.0 532.00 532.01 532.1 532.10 532.11 532.2 532.20 532.21 532.3 532.30 532.31 532.4 532.40 532.41 532.5 532.50 532.51 532.6 532.60 532.61 532.7 532.70 532.71 532.9 532.90 532.91 533 533.0 533.00 533.01 533.1 533.10 533.11 533.2 533.20 533.21 533.3 533.30 533.31 533.4 533.40 533.41 533.5 533.50 533.51 533.6 533.60 533.61 533.7 533.70 533.71 533.9 533.90 533.91 534 534.0 534.00 534.01 534.1 534.10 534.11 534.2 534.20 534.21 534.3 534.30 534.31 534.4 534.40 534.41 534.5 534.50 534.51 534.6 534.60 534.61 534.7 534.70 534.71 534.9 534.90 534.91 |
| Mild liver disease | 1 | 571.0 571.1 571.40 571.41 571.49 571.5 571.6 571.9 |
| Diabetes mellitus without complications | 1 | 249 249.0 249.00 249.01 249.10 249.2 249.20 250.0 250.00 250.01 250.02 250.03 250.20 250.21 250.22 250.23 |
| Diabetes mellitus with complications | 2 | 249.50 249.60 249.70 250.1 250.10 250.11 250.12 250.13 250.3 250.30 250.31 250.32 250.33 250.4 250.40 250.41 250.42 250.43 250.5 250.50 250.51 250.52 250.53 250.6 250.60 250.61 250.62 250.63 250.7 250.70 250.71 250.72 250.73 250.8 250.80 250.81 250.82 250.83 250.9 250.90 250.91 250.92 250.93 357.2 362.01 362.02 362.03 362.04 362.05 362.06 362.07 366.41. |
| Hemiplegia or paraplegia | 2 | 342 342.0 342.00 342.01 342.02 342.1 342.10 342.11 342.12 342.8 342.80 342.81 342.82 342.9 342.90 342.91 342.92 344.0 344.00 344.01 344.02 344.03 344.04 344.09 344.1 344.2 344.3 344.30 344.31 344.32 344.4 344.40 344.41 344.42 344.5 438.2 438.20 438.21 438.22 438.3 438.30 438.31 438.32 438.4 438.40 438.41 438.42 |
| Moderate / severe chronic kidney disease | 2 | 580.0 580.4 580.8 580.81 580.89 580.9 582 582.0 582.1 582.2 582.4 582.81 582.89 582.9 583 583.0 583.1 583.2 583.4 583.6 583.7 583.8 583.81 583.89 583.9 585 585.1 585.2 585.3 585.4 585.5 585.6 585.9 586 588 588.0 588.1 588.8 588.81 588.89 588.9 |
| Non-metastatic solid tumour or leukaemia and lymphoma | 2 | 140 140.0 140.1 140.3 140.4 140.5 140.6 140.8 140.9 141 141.0 141.1 141.2 141.3 141.4 141.5141.6 141.8 141.9 142 142.0 142.1 142.2 142.8 142.9 143 143.0 143.1 143.8 143.9 144 144.0 144.1 144.8 144.9 145 145.0 145.1 145.2 145.3 145.4 145.5 145.6 145.8 145.9 146 146.0 146.1 146.2 146.3 146.4 146.5 146.6 146.7 146.8 146.9 147 147.0 147.1 147.2 147.3 147.8 147.9 148 148.0 148.1 148.2 148.3 148.8 148.9 149 149.0 149.1 149.8 149.9 |
| Moderate / severe liver disease | 3 | 456.0 456.1 456.2 456.20 456.21 571.2 571.4 571.42 571.8 572.2 572.3 572.4 572.8 573.5 |
| Metastatic solid tumour | 6 | 196 196.0 196.1 196.2 196.3 196.5 196.6 196.8 196.9 197 197.0 197.1 197.2 197.3 197.4 197.5 197.6 197.7 197.8 198 198.0 198.1 198.2 198.3 198.4 198.5 198.6 198.7 198.8 198.81 198.82 198.89 199 199.0 199.1 199.2 |
| AIDS | 6 | “042” |

Upon the definition of each patient's conditions, the ICD-9 (International Classification of Diseases, 9th version – used in the GDH database) codes were obtained (Table 1).

Social and demographic data (patient's age and gender) were obtained for each admission episode corresponding to hospital admissions during 2015, in addition to the 22 conditions classified according to the ICD-9 system (Table 1).

Data were exported to Excel and subsequently to SPSS, version 24.0 IBM software for Mac OS.

The paediatric population (ages 0-17) was removed from exported data and, considering that each patient could have been admitted to hospital more than once per year, duplicate entries regarding the adult population (aged 18 or over) have been also removed and only the most recent admission episode has been considered for each patient.

The 22 conditions were dichotomised and the value of 1 corresponded to the presence and 0 to the absence of each condition. The number of conditions within a patient corresponded to the sum of the medical conditions that were presented by each patient. Multimorbidity was determined according to the settings of the coexistence of two or more conditions (MM2+) up to eight or more (MM8+).

An overall index score was obtained, considering the weight assigned to conditions within the scale (Table 1). This index was adjusted to patient's age, through the following weighting: 1 for the 40-49 age group; 2 for the 50-59; 3 for the 60-69 and 4 for the 70+ age group.

Patient's age, the number of conditions within a patient and Charlson index were taken into consideration in the descriptive analysis as numerical variables and these were categorised in order to make the analysis easier:

1. Age groups: early adulthood [18-39], middle adulthood [40-54], pre-retirement adulthood [55-64], third age [65-74], fourth age [75-84] and fifth age [85 +].
2. Total number of conditions within a patient: according to the definition of multimorbidity, two or more (MM2+) up to eight or more (MM8+).
3. Charlson index per severity of illness: age-adjusted [cut-off point 0 to < 5; 5 to < 9; ≥ 9] or non-age-adjusted [cut-off point < 5; ≥ 5].

Due to the binary nature of variables, the analysis was carried out by using a generalised linear model (GLM) with binary logistic regression.

Bivariate analysis was obtained for each condition and for each definition of multimorbidity, as dependent variables.

### Ethical requirements

The GDH database, provided with encrypted personal identification data, is provided to the students of the ENSP (*Escola Nacional de Saúde Pública*) upon application for superior authorisation and non-disclosure agreement.

The study was approved by the Ethics Committee of the *Administração Regional de Saúde de Lisboa e Vale do Tejo.*

## RESULTS

A total of 1,026,317 hospital admission episodes were exported from the GDH database, 136,574 of which corresponded to paediatric patients. Duplicate episodes were removed according to the methodology and only the most recent admission episode has been considered for each patient; upon removal of 10% of the episodes, a total of 800,376 episodes involving adult patients were considered [58% involving female patients – 463,978; mean age of 59.8 years, higher in male (62.3 years) than female patients (57.9 years)].

Data distribution per age group and gender is shown in Table 2 (patients admitted to a public hospital at least once in 2015).

A female predominance has been found in all age groups, except in the 65-74 (51% male patients).

A 1.6 average number of conditions per patient have been found (1.8 in male and 1.44 in female patients). A higher disease severity obtained with the Charlson index was also found in male patients (1.11) compared to 0.74 in female patients and 0.90 in the study sample. A decline in all age groups of the frequency of multimorbidity for different settings [two (MM2+) to eight conditions (MM8+) within a patient] has been found as progressing from MM2+ to MM8+: 41.9% (MM2+), 28.0% (MM3+), 18.4% (MM4+),

Table 2 – Age group and gender

| Age group | Male | | Female | | Total | Total |
|---|---|---|---|---|---|---|
| Early adulthood [18-39] | 43,263 | 26.80% | 117,971 | 73.20% | 161,234 | 100.00% |
| Middle adulthood [40-54] | 58,930 | 41.20% | 84,224 | 58.80% | 143,154 | 100.00% |
| Pre-retirement adulthood [55-64] | 61,524 | 49.80% | 62,018 | 50.20% | 123,542 | 100.00% |
| Third age [65-74] | 74,859 | 51.00% | 71,783 | 49.00% | 146,642 | 100.00% |
| Fourth age [75-84] | 70,507 | 46.50% | 81,210 | 53.50% | 151,717 | 100.00% |
| Fifth age [85+] | 27,315 | 36.90% | 46,772 | 63.10% | 74,087 | 100.00% |
| Total | 336,398 | 42.00% | 463,978 | 58.00% | 800,376 | 100.00% |

12.4% (MM5+), 8.8% (MM6+), 5.0% (MM7+) and 3.1% (MM8+).

No statistically significant association between multimorbidity and patient's age or severity of illness (Charlson index) has been found. An increasing average number of conditions and Charlson index values have been found up to the 85-89 age group. A decline in both multimorbidity measures was found from the age 90 onwards.

Considering that the frequency of medical conditions is based on the list of conditions considered within the methodology and those found in literature as most frequent, their association with patient's gender was analysed, adjusted to patient's age.

Conditions associated with patient's gender in age-adjusted bivariate analysis are shown in Table 3 by descending order of odds ratio (OR). Non-metastatic solid tumour or leukaemia and lymphoma, liver disease and peripheral vascular disease stood out in male patients, while osteoporosis, connective tissue disease and depression stood out in female patients.

Anxiety (OR 2.016) and depression (OR 3.972) were associated ($p < 0.001$) with younger age (45-64 age group), while congestive heart failure (OR 223.701), moderate/severe chronic kidney disease (OR 44.240) and dementia (OR 1,864.620) were associated with older ages (95+ age group), with the same significance level ($p < 0.001$). Liver disease (OR 9.929) and metastatic cancer (OR 12.629) showed an association with middle age groups (55-64). Hypertension and coronary artery disease were considered as having an increasing OR from the age of 65 onwards. The lowest number of conditions associated with the risk of mortality (OR > 1) was found in the youngest age groups (up to the age of 45).

Multivariate analysis of conditions associated with severity of illness (Charlson ≥ 5) as dependent variables has been carried out. All conditions were adjusted to patient's gender, age and number of conditions within a patient and, as shown in Table 4, the number of conditions within a patient was the highest predictor of severity of illness followed by dementia, diabetes mellitus, COPD and congestive heart failure, by descending order of the value of OR. A protective effect of female gender [$p < 0.001$; OR 0.807 (0.773: 0.842)] while a risk effect of patient's age were suggested [$p < 0.001$; OR 1.713 (1.703: 1.724)].

Conditions that were included due to their frequency and that were not included as candidate conditions in the Charlson index were not associated with severity of illness (Charlson ≥ 5). Nevertheless, a significant association with the overall index score ($p < 0.001$) (OR close to 0) with an apparent protective effect was found with conditions that were not included as candidate conditions within the Charlson scale (osteoarthritis, osteoporosis, anxiety, depression, hypertension, dyslipidaemia and obesity).

Bivariate analysis has been carried out, in order to assess the association between multimorbidity and severity of illness scores (Charlson index) through the GLM model.

Table 3 – Conditions associated with patient's gender

| Condition | *p* | OR | Lower range | Upper range |
|---|---|---|---|---|
| **Male gender** | | | | |
| Non-metastatic solid tumour or leukaemia and lymphoma | < 0.001 | 5.276 | 4.838 | 5.753 |
| Liver disease | < 0.001 | 2.813 | 2.719 | 2.910 |
| Peripheral vascular disease | < 0.001 | 2.797 | 2.706 | 2.891 |
| Coronary artery disease | < 0.001 | 2.205 | 2.132 | 2.280 |
| COPD | < 0.001 | 2.175 | 2.124 | 2.227 |
| Peptic ulcer | < 0.001 | 1.973 | 1.876 | 2.075 |
| Moderate / severe renal disease | < 0.001 | 1.483 | 1.457 | 1.510 |
| Metastatic solid tumour | < 0.001 | 1.482 | 1.449 | 1.515 |
| Diabetes mellitus | < 0.001 | 1.311 | 1.295 | 1.327 |
| Cerebrovascular disease | < 0.001 | 1.205 | 1.181 | 1.228 |
| Dyslipidaemia | < 0.001 | 1.150 | 1.137 | 1.163 |
| Hypertension | < 0.001 | 1.072 | 1.061 | 1.083 |
| Congestive heart failure | < 0.001 | 1.065 | 1.048 | 1.083 |
| **Female gender** | | | | |
| Osteoporosis | < 0.001 | 6.738 | 6.304 | 7.203 |
| Connective tissue disease | < 0.001 | 2.775 | 2.632 | 2.925 |
| Depression | < 0.001 | 2.766 | 2.706 | 2.827 |
| Osteoarthritis | < 0.001 | 1.695 | 1.658 | 1.732 |
| Anxiety | < 0.001 | 1.517 | 1.463 | 1.573 |
| Obesity | < 0.001 | 1.384 | 1.360 | 1.408 |
| Dementia | < 0.001 | 1.202 | 1.173 | 1.232 |

When severity categories of the age-adjusted Charlson index were used [cut-off 5 to < 9 (severe) and cut-off ≥ 9 (very severe)], a different association between multimorbidity and severity of illness has been found (Table 5) with an increasing association from the presence of six conditions onwards with the two poorest outcome cut-offs, particularly with ≥ 9.

No association with the highest severity cut-off of the Charlson index (≥ 9) has been found up to MM5+ (five conditions or more) and a conflicting trend of association with the cut-off 5 to < 9 has been found. From MM6+ onwards, a consistently increasing OR for both severity cut-offs has been found.

## DISCUSSION

The higher average number of conditions,[1,8] in male patients found in this study is worth mentioning,[1,8] as well as the severity of illness through the Charlson index.[1,11] A variable frequency of multimorbidity has been confirmed for different settings (MM2+ to MM8+) with a declining frequency in all age groups when progressing from MM2+ to MM8+: 41.9% (MM2+), 28.0% (MM3+), 18.4% (MM4+), 12.4% (MM5+), 8.8% (MM6+), 5.0% (MM7+) and 3.1% (MM8+). These results were slightly lower to those found in the Australian study, except regarding MM2+,[9] probably due to the fact that data regarding hospitalised patients were used. A decline in the whole multimorbidity scores has been found in most elderly patients (≥ 90).

A so-called clinical coherence was granted by conditions associated with male gender (liver disease or COPD, for instance)[27,28] as based on the empiric knowledge and confirmed by literature.[29-36] The same applies to the association of conditions associated with female gender: musculoskeletal disorders[37] (osteoporosis[38] and connective tissue disease) and mental disorders[37] (dementia, anxiety and depression). The associations of health conditions such as congestive heart failure and dementia with elderly ages are in line with literature.[39]

A relationship between multimorbidity and severity of illness has not been clearly established and therefore the Charlson index was used (outcome instrument) as a measure of severity of illness.[16,20] Scores such as the Charlson index allow for the aggregation of the complex reality into single indicators, with a list of conditions weighted according to the mortality risk. Despite the controversy regarding the use of scores,[17] the use of the Charlson index was confirmed as clinically relevant and useful in further comparisons

Table 4 – Conditions associated with Charlson index ≥ 5, non-adjusted to patient's age in multivariate analysis

| Diagnosis | *p* | OR | Lower range | Upper range |
|---|---|---|---|---|
| Corrected total of conditions | < 0.001 | 804.571 | 737.763 | 877.430 |
| Dementia | < 0.001 | 379.468 | 326.066 | 441.617 |
| Diabetes mellitus | < 0.001 | 156.458 | 143.129 | 171.028 |
| COPD | < 0.001 | 111.830 | 100.183 | 124.832 |
| Congestive heart failure | < 0.001 | 103.997 | 94.112 | 114.921 |
| Non-metastatic solid tumour or leukaemia or lymphoma | < 0.001 | 89.627 | 70.070 | 114.643 |
| Connective tissue disease | < 0.001 | 86.283 | 73.785 | 100.897 |
| Peptic ulcer | < 0.001 | 70.029 | 57.713 | 84.974 |
| Cerebrovascular disease | < 0.001 | 64.745 | 58.290 | 71.915 |
| Peripheral vascular disease | < 0.001 | 40.663 | 35.344 | 46.783 |
| Moderate or severe renal disease | < 0.001 | 33.917 | 29.265 | 39.308 |
| Acute myocardial infarction | < 0.001 | 25.338 | 22.253 | 28.852 |
| Liver disease | < 0.001 | 24.303 | 20.324 | 29.062 |
| Hemiplegia or paraplegia | < 0.001 | 13.251 | 11.300 | 15.540 |

Table 5 – Association between measures of multimorbidity and categories of poorest outcome of the age-adjusted Charlson index

| Cut-off | 5 to < 9 | | | | ≥ 9 | | | |
|---|---|---|---|---|---|---|---|---|
| | *p* | OR | Lower range | Upper range | *p* | OR | Lower range | Upper range |
| MM2+ | < 0.001 | 52.641 | 51.697 | 53.602 | ns | | | |
| MM3+ | < 0.001 | 29.495 | 29.099 | 29.896 | ns | | | |
| MM4+ | < 0.001 | 39.407 | 38.690 | 40.137 | ns | | | |
| MM5+ | < 0.001 | 76.959 | 74.325 | 79.687 | ns | | | |
| MM6+ | < 0.001 | 209.546 | 192.851 | 227.685 | < 0.001 | 53,836.701 | 48,424.289 | 59,841.703 |
| MM7+ | < 0.001 | 473.172 | 376.402 | 594.822 | < 0.001 | 24,346.826 | 19,366.124 | 30,608.496 |
| MM8+ | < 0.001 | 1097.052 | 579.187 | 2110.751 | < 0.001 | 79,684.008 | 41,448.928 | 153,189.513 |

ns: not significant

between different settings.[14,18,19] The association of the poorest outcomes and conditions with the highest severity with male gender seems to confirm the 'morbidity-mortality (gender) paradox' suggesting that healthcare in male patients should be mainly focused on the deadliest health conditions such as cancer, heart or cerebrovascular diseases, while mainly on the approach to health conditions with a relevant impact on patient's functional capacity in female patients (musculoskeletal and mental disorders).[40,41]

The validity of the results obtained in our study may be due to the robustness given by the sample size, by the significance of results, the diagnostic accuracy as well as clinical coherence. The inclusion of accurate medical diagnoses and the use of medical records classified according to the International Classification of Diseases (ICD) coding system has been assumed as diagnostic accuracy. The use of medical records classified according to the ICD system has contributed to the reproducibility and external validity of the results, as well as to the comparability of morbidity between different countries[17] and settings.

The question arises as to whether this association with male gender is related with the source of data regarding severity of illness (hospital admission data), with gender paradox regarding the use of healthcare services or even with specific characteristics of the Portuguese population, due to the fact that an association between multimorbidity and male gender has been found, in line with the Portuguese study carried out in primary care setting.[11] However, these results are not in line with the meta-analysis by Violan C *et al.,* in which an association with female gender has been found by most studies.[13]

In line with the minimum number of medical conditions to be included in multimorbidity studies[4] in order to ensure the lowest possible variability,[6] a total of 22 conditions were included in our study, including the most frequently studied[4] such as diabetes mellitus, osteoarthritis, hypertension and cancer.[4] The GLM model of analysis and the use of the Charlson index were the other methodological strategies that make our study reproducible, even though it should not be extrapolated to the population, due to the use of hospital admission data.

The association between any measure of multimorbidity (from MM2+ to MM8+) and the Charlson index was confirmed with the assessment of the association between multimorbidity and severity of illness measure (Charlson index) through bivariate analysis within the GLM model. When the association between multimorbidity (MM2+ to MM8+) and three cut-offs of an age-adjusted Charlson index (< 5, 5 to < 9 and ≥ 9) was analysed, the poorest outcome was associated with the setting of six or more medical conditions. Despite the apparent clinical significance, this was not found in literature, even though it is questioned whether or not it corresponds to the concept of complex multimorbidity, defined as the "co-occurrence of three or more chronic conditions affecting three of more different systems within a patient".[9] Further studies are required to clarify the meaning of a multimorbidity setting of six or more conditions (MM6+) as a measure of severity of illness. The results obtained from the GLM model explain for the range of values of OR and confidence intervals (Table 5).

The number of conditions within a patient was the greatest predictor of the severity of illness followed by dementia, diabetes mellitus, COPD and congestive heart failure, by descending order of the value of OR, which seems in line with the decline in average life expectancy associated with multimorbidity, with a 1.8-year reduction related to each additional chronic condition (ranging between a 0.4-year reduction with the first condition and 2.6-year with the sixth).[17]

The cross-sectional design and the nature of the study have been identified as limitations of the study, in addition to the absence of socioeconomic data including patient's education, income or social network, which are consistently associated with multimorbidity in other studies,[12,13] or even the absence of protective factors reducing the effect of multimorbidity such as patient's high education, healthy lifestyle, good social network and regular leisure activity.[42]

According to the authors, the fact that the same medical conditions were used in both measures of multimorbidity and severity of illness (Charlson index) is the main limitation of the study. However, this study leaves the prospect that these issues would become more clarified with further research with longitudinal studies on the association between the number and nature of medical conditions and the use of Charlson index over time in different settings (admission to hospital, primary healthcare and general population). Further studies and models of analysis are required for the approach to the complexity of multimorbidity (social, mental and physical) and clarification of the currently simple definition of multimorbidity, which is apparently indadequate.[17]

Despite the limitations, different aspects make this study unique, including:

- The results were based on a robust database, such as the GDH database, involving conditions classified according to the ICD-9 system and allowing for the determination of severity through the Charlson index.
- The reproducibility of this methodology, with a contribution to further comparisons between healthcare departments, healthcare units or levels of healthcare.
- The size of our group of patients and the method of analysis, allowing for the confirmation of an association between severity of illness and multimorbidity with male gender.
- The association between severity of illness and the setting of six or more medical conditions within a patient may become a simple measure of severity of illness.

## CONCLUSION

Multimorbidity and severity of illness were associated with male gender. The results of the study have confirmed that further health interventions adapted to gender are required as more severe conditions were mainly found in male patients (cancer, liver and vascular diseases) while conditions associated with functional capacity (musculoskeletal and mental diseases) were mainly found in female

patients. The number or conditions, followed by dementia and diabetes mellitus were the greatest predictors of severity of illness by using the Charlson index. Multimorbidity with six or more conditions within a patient was consistently associated with severity of illness.

## HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

## DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

## CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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