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Comorbidity and in-hospital mortality in peritoneal dialysis patients: data of the Emilia Romagna region of Italy

F. FABBIAN[1,2], A. DE GIORGI[3], F. FERRARA[2], G. ALFANO[4], G. MORI[4], A. DI MARIA[2], M. FRISINA[4], M. VERONESI[1], A. STORARI[1], G. DONATI[4]

[1]Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[2]Nephrology and Dialysis Unit, University Hospital of Ferrara, Ferrara, Italy
[3]Clinica Medica Unit, University Hospital of Ferrara, Ferrara, Italy
[4]Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, Section of Nephrology, University of Modena and Reggio Emilia, Modena, Italy

Abstract. – OBJECTIVE: Kidney failure increases in-hospital mortality (IHM); however, comorbidity is crucial for predicting mortality in dialysis patients. Our aim was to evaluate the impact of comorbidity, assessed by modified Elixhauser index (mEI), Charlson Comorbidity Index (CCI), and age-adjusted CCI, on IHM in a cohort of peritoneal dialysis patients admitted to hospitals of the Emilia Romagna region (ERR) of Italy.

PATIENTS AND METHODS: All hospital admissions of peritoneal dialysis patients recorded between 2007 and 2021 in the ERR database were analyzed. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used for detecting diagnoses and procedures, and the inclusion criterion was code 5498. Comorbidity burden was evaluated by three different scores, and hemodialysis (HD) treatment need was considered. IHM was our outcome.

RESULTS: During the 15 years of the study, 3,242 hospitalized peritoneal dialysis patients (62.7% males) were evaluated. Mean age was 62.8±20.6 years, 9.6% underwent HD, and IHM was 5.9% (n=192). IHM mortality was stable throughout the study period. Deceased subjects were older, were hospitalized longer, had a higher comorbidity burden, and had a higher percentage of HD treatment needs than survivors. Age, male sex, comorbidity burden, and HD treatment were predictors of IHM. Receiver operating characteristics (ROC) analysis confirmed the impact of comorbidity burden on IHM, especially when age was considered.

CONCLUSIONS: We conclude that in male, elderly hospitalized peritoneal dialysis patients with failing dialysis technique, comorbidity burden should be considered being a predictor of IHM.

Key Words:
Peritoneal dialysis, Uraemia, Comorbidity, Charlson comorbidity index, Modified Elixhauser index, In-hospital mortality.

Introduction

Kidney failure increases the risk for in-hospital mortality (IHM), and this relationship involves different conditions such as cardio-renal syndrome[1,2], myocardial infarction[3], stroke[4], and chronic obstructive pulmonary disease[5]. On the other hand, considering comorbidity is crucial for predicting mortality in dialysis patients. In 2019, Anderson et al[6] wrote a systematic review and meta-analysis aiming at selecting articles describing validated prognostic indices predicting mortality in dialysis populations. Thirty-two prognostic scores were evaluated in 36 articles and predictive windows varied from three months to ten years. Charlson Comorbidity Index (CCI) was the most commonly used, however authors concluded that several validated scores predicted survival at the time of beginning of dialysis treatment[6].

In the last decades, different medical prediction models have been developed to improve clinical practice. However, external validity is necessary to recommend clinical use of prediction models. In 2017, external validation of prediction models for mortality in dialysis patients was assessed, and the performance of the models was poorer in the external validation than in the original population[7].

In 2019, it was shown that a modified version of Elixhauser index (mEI) was able to predict in-hospital mortality in a large nationwide Italian cohort of subjects suffering acute kidney injury[8].

The aim of this study was to assess the association of burden of comorbidity measured by a mEI[9], CCI[10] and age-adjusted CCI (ACCI)[11], and IHM in a large cohort of peritoneal dialysis patients admitted in the hospitals belonging to the Emilia Romagna region (ERR) of Italy.

Corresponding Author: Fabio Fabbian, MD; e-mail: f.fabbian@ospfe.it

Patients and Methods

We conducted a retrospective study in agreement with the Declaration of Helsinki, using a database in which personal data were deleted to maintain data anonymity and confidentiality. Ethics committee approval was not required because the study was conducted in agreement with the existent Italian disposition-by-law[12]. The Italian law states that observational studies do not require Ethics committee approval, but only notification is sufficient.

All hospital admissions of peritoneal dialysis recorded in the database of the ERR of Italy between January 1, 2007, and December 31, 2021, and maintained by the Center for Health Statistics were included. ERR belongs to North-East of Italy with a total population of around 4,400,000 (~7% of the country). All Discharge Hospital Sheets (DHS) of patients admitted to all the regional hospitals have been stored in an electronic database since 1999.

Information contained in the DHS reports are sex, age, date and department of admission and discharge, vital status at discharge (in-hospital death *vs.* discharged alive), main diagnosis, up to five comorbidities, and up to six procedures/interventions. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) is used to classify diagnoses and procedures. Personal data and all other potential identifiers were removed from the database, following the national disposition-by-law in terms of privacy. A consecutive number for each patient was the only identifier, and every record corresponded to a single admission. In the case of patients admitted to one hospital and then transferred to another, only one admission was considered (with the date of hospitalization referring to the admission hospital and the final diagnosis made by the discharging hospital). Clinical information is not provided by the administrative regional database.

The study included only peritoneal dialysis patients, considering all admissions recorded from 2007 to 2021. All hospitalizations were analyzed as a single record so that one patient could have had different admissions. The inclusion criterion was the identification of the ICD-9-CM code 5498.

Data Analysis

Our only outcome was IHM. In order to evaluate the comorbidity burden, we used mEI[9], CCI[10] and ACCI[11].

Comorbidity Calculation

CCI predicts survival in patients with multiple comorbidities, as each condition has different weights, and the sum of the single scores associated with the presence of a specific disease is representative of a measure of total comorbidity burden. Overall, several diseases are included, such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS[10] (Table I). Since age has been subsequently determined to be associated with prognosis, Charlson et al[11] modified the scoring system with the addition of patients' age in 1994. ACCI incorporates age as a correction variable of the final score by adding one point for every decade over 40 years old (Table I). The original scores were corrected, removing the diagnosis of renal disease.

To calculate the mEI, the following conditions, based on administrative data, were considered: age, sex, neurological disorders, lymphoma, solid tumors with metastasis, ischemic heart disease, congestive

Table I. Points assigned to different conditions to calculate the Charlson Comorbidity Index (CCI) and age-adjusted CCI (ACCI). The ACCI incorporates age as a correction variable of the final score by adding 1 point for every decade over 40 years old. Points assigned to renal diseases in the original score were excluded.

Comorbidities	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immune-deficiency syndrome (AIDS)	6

Table II. Points are assigned to different conditions to calculate the modified Elixhauser index. Points assigned to renal diseases in the original score were excluded.

Comorbidities	Score
Age 0-60 (years)	0
Age 61-70 (years)	3
Age 71-80 (years)	7
Age 81-90 (years)	11
Age 91+ (years)	16
Male gender	2
Neurological disorders	3
Lymphoma	4
Solid tumor without metastasis	4
Ischemic heart disease	5
Congestive heart failure	5
Coagulopathy	8
Fluid and electrolyte disorders	8
Liver disease	10
Cachexia	11
Metastatic cancer	12

heart disease, coagulopathy, fluid and electrolyte disorders, liver disease, weight loss, and metastatic cancer. The original score was corrected, removing the diagnosis of renal disease (Table II).

Comorbidity scores were automatically calculated based on the guidelines suggested by Quan et al[13]. Finally, we also considered hemodialysis (HD) treatment (code ICD-9-CM 39.95) during hospitalization.

Statistical Analysis

A descriptive analysis of all data collected was performed, and absolute numbers, percentages, and mean ± SD were used to show results. By univariate analysis, we looked for differences between survivors and deceased subjects. Based on the type of data, statistical analysis was conducted with the Chi-square test for detecting differences in frequencies, and with Student *t*-test, and Mann-Whitney test for detecting differences between normally distributed or non-normally distributed data, respectively. We compared age, sex, length of stay, comorbidity burden, and the need for hemodialysis treatment during admission. Moreover, being IHM our outcome, it was considered the dependent variable in a multivariate logistic regression analysis, while demography, comorbidity scores, and hemodialysis treatment were the independent variables. We calculated three models in which the comorbidity burden was evaluated with the three different scores. Age was not considered in the models evaluating mEI and ACCI because the parameter was included in the score calculation. Odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated. Finally, the models were compared using receiver operating characteristics (ROC) curve scores (*c*-statistics). The probability of risk of death assigned is the *c*-statistics: if the value is 0.5, the model is not a good predictor, while a value of 1 suggests perfect discrimination between deceased and survivor individuals. Values lower than 0.7 are considered poor predictors, and those between 0.7 and 0.8 are reasonable. When the value is greater than 0.8, the prediction is good. The area under the receiver-operator characteristic curve (AUC) and 95% confidence intervals were calculated. Statistical Product and Service Solution (SPSS) 26.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. A two-sided $p < 0.05$ was considered significant.

Results

During the 15 years of the study, 3,242 peritoneal dialysis subjects were admitted to the different hospitals of the ERR of Italy, of whom 62.7% were males. Mean age was 61.8±20.6 years, the duration of hospitalization was 10.9±13.8 days, hemodialysis treatment was performed in 9.6% of the population, and IHM was 5.9% (n=192). Mean values of the three indexes are reported in Table III. Figure 1 shows the distribution of the comorbidity in the entire population. The percentage of IHM during the study period is displayed in Figure 2. Additionally, the number of peritonitis was 193 (5.9%). A comparison of survivors and individuals deceased during admission is present-

Table III. Demographic and clinical characteristics of the population.

Records	3,242
Males/females, n (%)	2,033/1,209 (62.7/37.3)
Age (years)	61.8±20.6
Length of hospitalization (days)	10.9±13.8
modified Elixhauser Index	6.9±5.4
Charlson Comorbidity Index	0.66±1.14
Age adjusted Charlson Comorbidity Index	3.34±2.01
Haemodialysis treatment, n (%)	310 (9.6%)

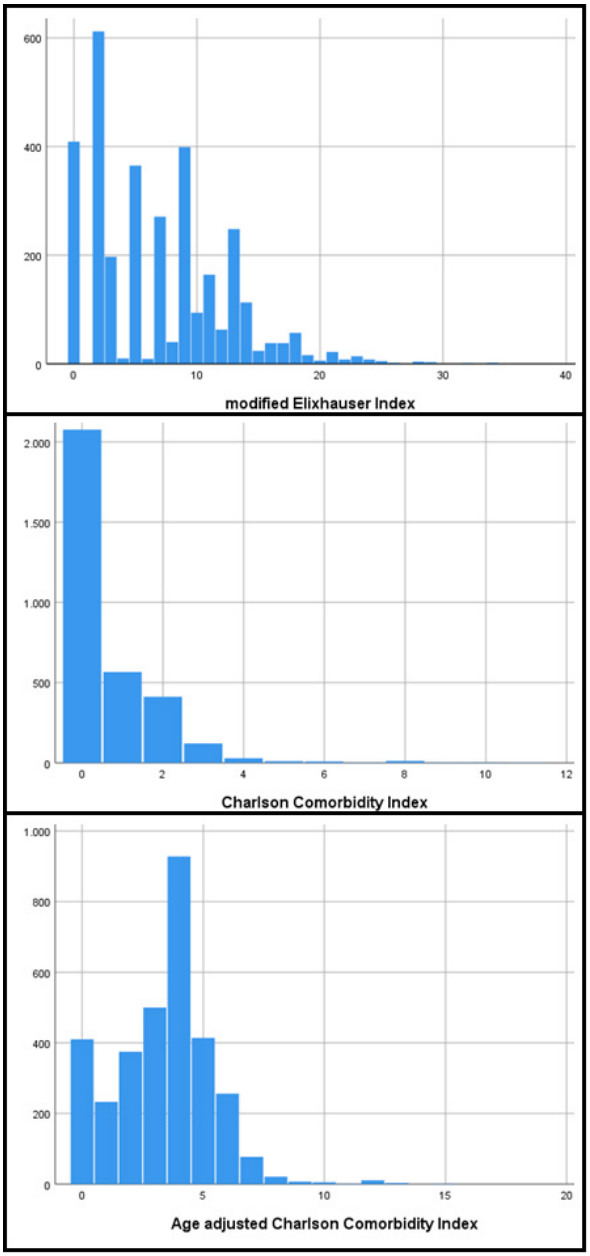

Figure 1. Distribution of the comorbidity in the peritoneal dialysis patients.

ed in Table IV. Subjects suffering IHM were more than 10 years older, were hospitalized for a longer time, had higher comorbidities burden, and needed HD treatment in more cases than individuals discharged alive. Factors independently associated with IHM in the population of peritoneal dialysis patients enrolled in this study are reported in Table V. Age, male sex, comorbidity burden evaluated with the three indexes, and HD treatment were predictors of IHM. Every increase in one point in comorbidity burden raised the risk of IHM by 13-17%. ROC analysis revealed an AUC was higher in the case of mEI being 0.760 (95% CI 0.727-0.792; $p<0.0001$) and lower in the case of CCI being 0.638 (95% CI 0.595-0.680; $p<0.0001$). The same value calculated for ACCI was 0.732 (95% CI 0.700-0.765; $p<0.0001$) (Figure 3).

Discussion

To the best of our knowledge, this is the first study that evaluates predictors of IHM in a large cohort of peritoneal dialysis patients followed up in a large region of Italy. Our retrospective analysis revealed that age, male sex, comorbidity burden, and the need for hemodialysis treatment were independently associated with IHM. The relationship between survival and characteristics of dialysis patients is an interesting debate. Factors that clinicians need to consider in order to predict mortality after dialysis initiation are still controversial.

In the uremic population, the outcome is generally poor, and it depends on several factors other than dialysis modality[14]. Therefore, the relationship between increasing age and survival during admission is not unexpected. Moreover, we found that men had a higher risk of all-cause mortality, in agreement with an observational cohort study from Northern Europe[15]. On the other hand, the impact of sex on negative outcomes needs to be further investigated in the peritoneal dialysis population.

Peritoneal dialysis treatment has been reported to be associated with a higher hospitalization rate, higher risk for first hospitalization, and higher risk of hospital admissions than hemodialysis therapy, being the crude hospitalization rate in peritoneal dialysis 2.3±5.0 per patient-year and peritonitis the main cause of admission[16]. Japanese peritoneal dialysis patients have high survival, as suggested by a study assessing data from the Japan Peritoneal Dialysis and Outcome Practice Patterns Study[17], including 808 adult peritoneal individuals. Median follow-up was 1.66 years, and mortality was 9.1%. All-cause and cardiovascular disease mortality were 5.1 and 1.7 deaths/100 patient-year, respectively. All-cause, peritonitis-related and cardiovascular-related hospitalization rates were 120.4, 21.1, and 15.6/100 patient-year, respectively. The median length of hospitalization was 19 days[17]. We cannot compare our results with these data; in fact, our mortality appears to be low. The great majority of patients evaluated were discharged alive.

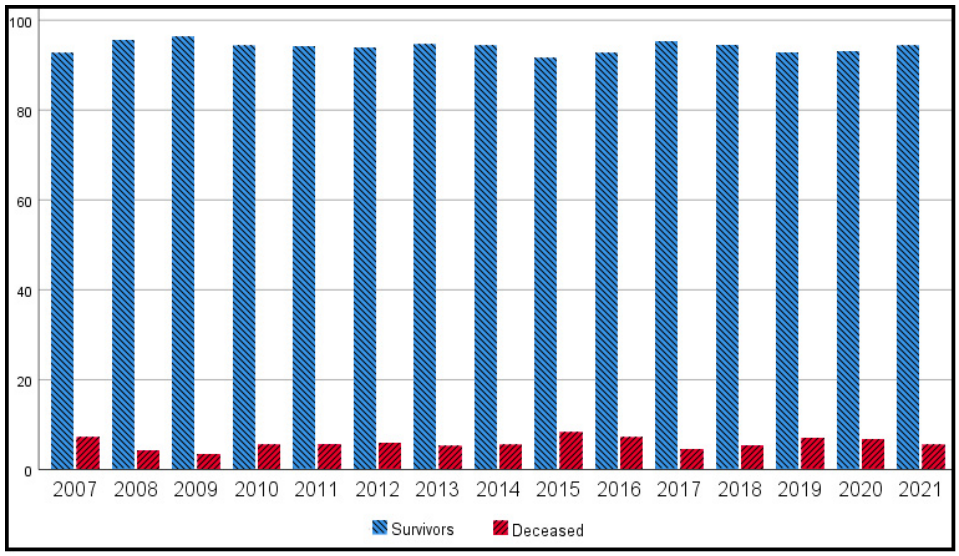

Figure 2. Percentage of survivors and deceased subjects during the 15 years of the study.

Table IV. Comparison of survivors and deceased peritoneal dialysis individuals.

	Survivors (n=3,050)	Deceased (n=192)	p
Males, n (%)	1,922 (37)	81 (42.2)	0.166
Females, n (%)	1,128 (63)	111 (57.8)	
Age (years)	61±20.6	74±16.2	<0.0001
Length of hospitalization (days)	10.3±12.8	20.3±23.3	<0.0001
modified Elixhauser Index	6.6±5.3	12.2±6.0	<0.0001
Charlson Comorbidity Index	0.61±1.08	1.32±1.77	<0.0001
Age adjusted Charlson Comorbidity Index	3.24±1.97	4.92±1.99	<0.0001
Haemodialysis treatment, n (%)	280 (9.2)	30 (15.6)	0.005

Table V. Factors independently associated with in-hospital mortality by means of multivariate analysis.

	OR	95% CI	p
Modified Elixhauser Index model			
Male sex	1.811	1.323-2.481	<0.0001
modified Elixhauser Index	1.170	1.142-1.199	<0.0001
Haemodialysis treatment	1.634	1.062-2.513	0.025
Age adjusted CCI model			
Male sex	1.381	1.018-1.875	0.038
Age adjusted CCI	1.469	1.367-1.577	<0.0001
Haemodialysis treatment	1.750	1.152-2.659	0.009
CCI model			
Age	1.052	1.038-1.065	<0.0001
Male sex	1.348	0.994-1.827	0.055
CCI	1.326	1.210-1.452	<0.0001
Haemodialysis treatment	1.772	1.165-2.695	0.008

CCI: Charlson Comorbidity Index.

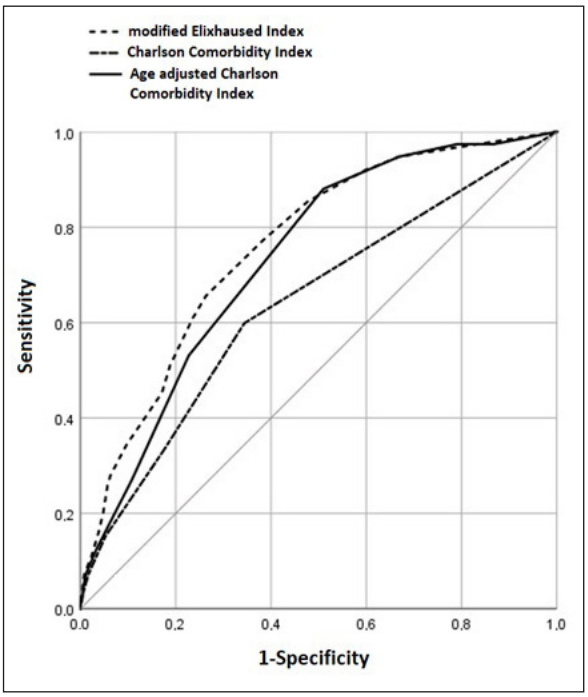

Figure 3. Receiver operating characteristics (ROC) analysis relating the comorbidity indexes to in-hospital mortality. The area under the curve (AUC) related to the modified Elixhauser Index is 0.760 (95% CI 0.727-0.792; $p<0.0001$), AUC related to ACCI is 0.732 (95% CI 0.700-0.765; $p<0.0001$) and AUC related to CCI is 0.638 (95% CI 0.595-0.680; $p<0.0001$).

On the other hand, the mean duration of hospitalization in deceased individuals was 20.3 days, not very different from Kawanishi's data[17]. Although our study design was different, our results are partially in agreement with the Peridialysis Study[18]. The Peridialysis Study enrolled 1,580 subjects and evaluated the first-year mortality in incident dialysis patients, and 61.6% of them were treated with peritoneal dialysis. The authors reported that first-year mortality was 13.33%. Independent factors predicting death were age, comorbidity, clinical contraindication to peritoneal dialysis or hemodialysis, suboptimal dialysis initiation, high glomerular filtration rate, low serum albumin, hyperphosphatasemia, high C-reactive protein, overhydration, and cerebral symptoms[18]. Moreover, in a recent study[19] analyzing data from Taiwan's National Health Insurance Database, the risk of major adverse cardiovascular events and all-cause mortality was high among peritoneal dialysis, especially in elderly, female, and diabetic patients. These studies did not evaluate the burden of comorbidity expressed by an index; however, authors did consider comorbidity and found that the latter was associated with death.

Our results suggest that hemodialysis treatment during admission represents a predictor of mortality during admission, suggesting that failure of peritoneal dialysis increases the risk of death in these patients. Sukul et al[20] studied transition rates from peritoneal dialysis to in-center hemodialysis, mortality, and transplantation in incident peritoneal dialysis patients recorded in the US Renal Data System from 1996 to 2015. Authors found that recent peritoneal dialysis patients had lower mortality and transition to in-center hemodialysis. A longer time of peritoneal dialysis treatment was associated with higher mortality, but a lower risk for transition to in-center hemodialysis, and larger peritoneal dialysis programs (≥25 *vs.* ≤6 patients) had a lower risk of death and transition to in-center hemodialysis[20]. A study[21] using data from Australia and New Zealand Dialysis and Transplantation Registry (ANZDATA), Canadian Organ Replacement Register (CORR), Europe Renal Association (ERA) Registry, and the United States Renal Dialysis System (USRDS) stated that the highest mortality was in the first month after a transfer from peritoneal dialysis to hemodialysis, underlying the vulnerability of patients at the time of modality transfer. Similar results were shown by Tsai et al[22], who assessed whether hemodialysis patients who transitioned from peritoneal dialysis had similar clinical outcomes as exclusively hemodialysis-treated subjects. They concluded that the transition from peritoneal dialysis to hemodialysis increased the risk of death[22].

Comorbidity is defined as one or more illnesses coexisting with an index disease of interest. The two well-known methods that summarize comorbidity are CCI[10] and EI[23]. Comorbidity may delay and confound diagnosis and impact mortality. CCI[10] appeared in 1987 and considers 16 diseases weighted on the strength of their association with mortality. EI[23] identified 30 comorbidities having an impact on short-term outcomes, however, no weight was assigned to each condition, assuming that all diseases were equally important for determining the outcome. mEI could be considered derived from the two previous indexes[9].

Thorsteinsdottir et al[24] studied prognostic indexes using retrospective cohort data in incident dialysis patients aged 81.5 years, with a median survival of 351 days. They concluded that most predictive scores for mortality performed moderately[24]. In the peritoneal dialysis population, CCI and its modified version were associated with mortality[25]. It was reported that for every increasing unit of the score, the relative risk of death was 1.54[26]. Chan et al[27] demon-

strated that the major reason for hospitalization of peritoneal dialysis patients was the implantation of a peritoneal catheter and its complications (23.22%). Our data are difficult to compare with those derived from the literature, being exclusively related to hospital admissions. However, they show that the measurement of comorbidity burden does matter. Recently, Noh et al[28] reported that comorbidity evaluated by modified CCI was a strong predictor of mortality, with a survival hazard ratio of 4.61 and an AUC 0.804[28]. Moreover, CCI was independently associated with 30-day readmission in a population of more than 124,000 patients treated with both hemodialysis and peritoneal dialysis[29]. Our results show that comorbidity, evaluated with three different indexes, predicts IHM. ROC analysis underlined that the highest AUC was obtained from mEI, although the performance was similar to ACCI, whilst the AUC was lower when CCI was used. These results could be ascribed to the fact that CCI calculation does not consider age.

Limitations

Different limitations of this study should be considered. First, this is a retrospective observational study based on ICD-9-CM codes, and low sensitivity and specificity are the major limitations of studies based on such codes. Second, we evaluated only all-cause mortality, and we did not analyze different causes for mortality, however, all-cause mortality is generally considered a hard outcome, being a parameter suggesting the effectiveness of interventions. Third, our study did not include clinical characteristics, we based our results only on the burden of comorbidity, calculated by ICD-9-CM codes. We could not consider clinical severity, functional and cognitive status, or intensity of care given, moreover, we could not evaluate the reason for treating patients with HD during admission, including dropout. In the same way, some comorbidities could have been disregarded, because of lack of recording. Accuracy and completeness of data are essential for calculating the true comorbidity index; therefore, data could reduce the performance of a comorbidity score and its ability to predict the outcome[30]. Fourth, due to the study design, no adjustments were made on important renal clinical parameters such as duration of chronic kidney disease, timing of nephrologists' care, and biochemical features. Again, specific renal replacement therapy characteristics such as prior and time spent on a specific renal replacement therapy modality and technique failure, late referral to a nephrology service, the transition between dialysis modalities, nutritional state, and residual renal function were overlooked[31,32]. On the other hand, a study from Australia and New Zealand, performed between 2000 and 2014, stated that peritoneal dialysis was associated with a reduced risk of early technique failure[33]. Besides, we ignored renal diagnosis. Primary kidney disease was demonstrated to impact the effect of comorbidities on the survival of subjects receiving long-term renal replacement therapy. Helve et al[34] reported that the risk of death was increased threefold in patients with uremia due to polycystic kidney disease and glomerulonephritis, while in subjects with uremia secondary to different kidney diseases, the risk of death increased less than twofold[34]. However, our study was limited to estimating predictors of IHM.

Conclusions

Peritoneal dialysis presents several advantages compared with hemodialysis, it can be carried out at home since it doesn't require frequent medical examinations, and it provides continuous therapy. Furthermore, it requires fewer restrictions on diet and fluid intake which is essential for a better quality of life due to fewer negative side effects such as nausea, vomiting, cramping, and weight gain than hemodialysis. It allows greater flexibility and freedom in the treatment schedule. On the other hand, peritoneal dialysis needs to be carried out every day, and patients could find it upsetting. Besides, the peritoneal catheter could be uncomfortable. Another major disadvantage of peritoneal dialysis is the risk of developing peritonitis. In rare cases, the peritoneum may gradually become thickened and scarred with progressive loss of function up to the need to switch to hemodialysis. Finally, peritoneal dialysis needs ample home storage space for supplies and requires responsibility and detailed training.

Besides these technical aspects, the comorbidity burden of hospitalized peritoneal dialysis patients should be considered, especially in elderly, male subjects, and those undergoing failing dialysis techniques. To the best of our knowledge, this is the first large cohort study of peritoneal dialysis patients treated in different nephrology units belonging to a large region of Italy; it found that age, male sex, comorbidity burden and the need for hemodialysis treatment were independently associated with mortality during hospitalization. Further studies are needed to validate these results in different hospital settings.

Conflict of Interest
Authors declare that they have no conflict of interest.

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Informed Consent
This retrospective cohort study was conducted in agreement with the declaration of Helsinki of 1975, revised in 2013. In order to maintain data anonymity and confidentiality, patient identifiers were canceled before data analysis, deleting the possibility of identification of subjects, either in this paper or in the database. Therefore, informed consent was not required. The study was carried out in agreement with the existent Italian disposition-by-law (G.U. No. 76, 31 March 2008).

Ethics Approval
The study was based on hospital data obtained consulting clinical records, and in agreement with the existent Italian disposition-by-law (G.U. No. 76, 31 March 2008), ethical approval was not required.

Availability of Data and Materials
The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author at reasonable request.

ORCID ID
Fabio Fabbian: 0000-0001-5189-3695
Alfredo De Giorgi: 0000-0002-0903-7825
Gaetano Alfano: 0000-0002-9479-2760
Giacomo Mori: 0000-0002-6668-2548
Gabriele Donati: 0000-0001-8549-1221

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Authors' Contributions
Conceptualization, F.F., A.D.G., G.D.; Methodology, A.D.G., F.F., G.A., G.M., A.D.M., M.F., M.V., A.S.; Literary analysis, A.D.G., F.F., G.A., G.M., A.D.M., M.F., M.V., A.S.; Resources, F.F., A.D.G., G.D.; Writing- original draft preparation, A.D.G., F.F., G.A., G.M., A.D.M., M.F., M.V., A.S.; Writing- review and editing, F.F. and G.D.; Supervision, F.F., and G.D.; Project administration, F.F., A.D.G., and G.D.; Funding acquisition, F.F. All authors have read and agreed to the published version of the manuscript.

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