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GESTION HOSPITALARIA Y COMPLICACIONES EN EL PACIENTE COMÓRBIDO

HOSPITAL MANAGEMENT AND COMPLICATIONS IN COMORBID PATIENTS

FABIO FABBIAN, MD

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TITULO: *Gestión hospitalaria y complicaciones en el paciente comórbido*

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HOSPITAL MANAGEMENT AND COMPLICATIONS IN COMORBID PATIENTS

Tesis Doctoral presentada en la Universidad de Córdoba

Directores:
Dr. Pablo Jesús López Soto
Dra. Maria Aurora Rodriguez Borrego (jubilada 26.6.2019)

Córdoba, España, 2019

TÍTULO DE LA TESIS: Gestión hospitalaria y complicaciones en el paciente comórbido.

DOCTORANDO/A: Fabio Fabbian

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

En un mundo cambiante la Salud es un reto y en ese contexto el abordaje de la Comorbilidad lo es doble.

En el grupo de investigación "*Cuidados Enfermeros Integrales Perspectiva multidisciplinar*" en cuyo seno se ha desarrollado el trabajo de Investigación, entre sus objetivos se encuentra "Una visión amplia e integral del ser humano y su vivencia de la salud y la enfermedad", visión requerida para el abordaje de la Comorbilidad en la que los registros y su calidad no son una cuestión baladí.

El doctorando, Médico Especialista en Nefrología trabajando en una Unidad de Medicina Interna está ampliamente implicado en el abordaje de ese doble reto. Experiencia que viene sustentada por amplia producción científica. En el *APPENDIX I* (*Table A: Publications*; Table B: *Conference Presentations*) del documento de la tesis, se presenta un extracto referido a los años 2018-2019.

Por todo lo expuesto, el director de la tesis refrenda que la misma cumple los requisitos formales de calidad y originalidad, mantiene el rigor científico y académico exigible, y viene respaldada por comunicaciones científicas en congresos y publicaciones, por lo que se autoriza la presentación de la tesis doctoral.

Córdoba, 1 de septiembre de 2019

Firma del director

Fdo.: Pablo Jesús López Soto

Fabio Fabbian, MD

To Raffaella, Margherita, Rodolfo, Marta and Roberto

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Questo lavoro è il coronamento di un intervallo temporale che è stato esaltante e mi ha visto assumere ruoli per me impensabili. Ringrazio il professor Pablo Jesús López Soto e la professoressa María Aurora Rodríguez Borrego per la possibilità di conseguire questo prestigioso titolo. E' un titolo che mi sento di condividere con le due persone con le quali ho percorso diverse tappe della mia recente vita, Roberto ed Alfredo. Roberto è il miglior direttore che chi ha voglia di scrivere possa avere, una mente brillante e stimolante, mai a riposo. Anche solo pochi minuti di dialogo possono stimolare idee che faticavano a concretizzarsi. Alfredo oltre che un ottimo medico, è un analista eccezionale, capace di vedere tra infiniti numeri, un filo conduttore. Senza le sue analisi "salentine", il mio traguardo sarebbe ancora lontano. Ringrazio i colleghi della clinica medica Benedetta, Christian, Elisa e Ruana che mi hanno sopportato anche quando troppo convinto della mortalità intra-ospedaliera. Ringrazio gli studenti ora dottori e quelli che rimangono a lungo studenti, che mi hanno continuamente stimolato. Ringrazio gli infermieri, Stefano, Isabella, Mauro e tutti quelli che non ho citato. Ringrazio infine coloro che da un punto di vista geneico per il 50% mi sono uguali, Margherita, Rodolfo, Marta e Roberto e soprattutto mia moglie Raffaella che ha sopportato le mie lunghe assenze da casa perché impegnato in ospedale, e nonostante questo mi ha sempre sostenuto.

This work is the culmination of a time interval that was exciting and during which I could gain a role that was unthinkable. I thank Professor Pablo Jesús López Soto and Professor María Aurora Rodríguez Borrego for the opportunity to achieve this prestigious title. It is a title that I can share with the two people with whom I have shared several steps of my recent life, Roberto and Alfredo. Roberto is the best manager that anyone who wants to write can have, a brilliant and stimulating mind, never at rest. Even just a few minutes of dialogue can stimulate ideas that were struggling to materialize. Alfredo as well as an excellent doctor, is an exceptional analyst, able to see a common thread in infinite numbers. Without his "Salentine" analyses, my goal would still be far away. I thank the colleagues of the unit Benedetta, Christian, Elisa and Ruana who have supported me even when I was too convinced about intra-hospital mortality. I thank the students now doctors and those who remain students for a long time, who have continuosly stimulated me. I thank the nurses, Stefano, Isabella, Mauro and all those I have not mentioned. Finally, I thank those who, from a genetic point of view, are 50% identical to me, Margherita, Rodolfo, Marta and Roberto, and above all my wife Raffaella, enduring my long absences from home because I was in hospital, and despite this she has always supported me.

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LIST OF ABBREVIATIONS

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€	Euro
£	Pound sterling
$	American dollar
%	Percentage
<	less than
>	higher than
≤	less or equal than
≥	higher or equal than
≈	approximately
±	more less
95% CI	95% Confidence Intervals
AARD	Acute Aortic Dissection or Rupture
AD	Alzheimer Disease
ADL	Activities of Daily Living
AEVB	Acute Esophageal Variceal Bleeding
AF	Atrial fibrillation
AKI	Acute Kidney Injury
APACHE	Acute Physiology and Chronic Health Evaluation
AUC	Area Under the Curve
CCI	Charlson Comorbidity Index
cEI	corrected Elixhauser Index
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular disease
CVE	Cardiovascular event
DHR	Discharge Hospital Records
DHS	Discharge Hospital Sheets
dl	deciliters
DRG	Diagnosis Related Groups
E	Escherichia
ECOG	Eastern Cooperative Oncology Group
ED	Emergency Department
e.g.	For example
EI	Elixhauser Index

ESRD	End-Stage Renal Disease
EUR	Euro
GP	General practitioner
GPs	General practitioners
GRD	Grupos de Diagnósticos Relacionados
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDR	Hospital Discharge Records
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD-10-CM	International Classification of Diseases, 10^{th} Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, 9^{th} Revision, Clinical Modification
ICED	Index of Coexistent Disease
ICU	Intensive Care Unit
i.e.	id est; namely
IHD	Ischemic Heart Disease
IHM	In-Hospital Mortality
IMW	Internal Medicine Ward
IRR	Interrater Reliability
KFC	Kaplan-Feinstein Classification
LEA	Livelli essenziali di assistenza
LOS	Length Of Stay
MEDS	Mortality in Emergency Department Sepsis
MEWS	Modified Early Warning Score
mg	milligrams
MI	Myocardial Infarction
MIH	Mortalidad Intrahospitalaria
mMEDS	modified Mortality in Emergency Department Sepsis
MPI	Multidimensional Prognostic Index
MRSA	Methicillin-resistant Staphylococcus Aureus
N	Number (sample)
n	Number (part of sample)
NEWS	National Early Warning Score
NHS	National Health Service
NS	Non-significance
OR	Odd Ratio
ORs	Odds Ratios

P	Pseudomonas
P	P-value
PCPs	Primary Care Physicians
PE	Pulmonary Embolism
PEs	Pulmonary Embolisms
PIRO	Predisposition, Infection, Response and Organ dysfunction
PPV	Positive Predictive Value
PROFUND	Index with a prognostic prediction applied to multi-pathological patients
PTLD	Post-Transplant Lymphoproliferative Disorders
REMS	Rapid Emergency Medicine Score
RER	Region Emilia Romagna
ROC	Receiver Operating Characteristic
RR	Risk Ratio
RTR	Renal Transplant Recipients
SC	Skin Cancers
SCS	Simple Clinical Score
SD	Standard deviation
SE	Sensitivity
SOC	Solid Organ Cancers
SP	Specificity
SPSS	Statistical Package for the Social Science
UTIs	Urinary Tract Infections
U.S.	United State
vs	versus
WD	Weekday
WE	Weekend
WHO	World Health Organization
yrs	years

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RESUMEN

INTRODUCCIÓN

La carga de comorbilidades parece estar relacionada con los resultados clínicos en pacientes hospitalizados y la estratificación clínica de los pacientes ingresados podría derivarse utilizando bases de datos administrativas. El objetivo principal de los datos administrativos es obtener retorno de información, no están planificados para la investigación clínica, por lo tanto, cuando se utilizan con fines clínicos, deben evaluarse cuidadosamente porque los temas de interés no pueden definirse con precisión. Por otro lado, las bases de datos administrativas tienen varias ventajas, como la cobertura de la población, el tamaño de muestra muy grande, la heterogeneidad de la población cubierta (perspectiva del "mundo real"), largos períodos de observación, información actualizada, sin costos adicionales para recopilar datos, posibilidad de vincular varias fuentes de información (por ejemplo, hospitalizaciones, atención ambulatoria, recetas de medicamentos, estado vital). Durante la última década, el grupo de investigación de la Unidad Clinica Médica del University Hospital Santa Anna (Ferrara, Italy) ha publicado varios artículos que relacionan bases de datos administrativas con condiciones clínicas.

OBJETIVOS

General

Evaluar la importancia de las comorbilidades recodificadas durante la hospitalización en bases de datos administrativas para comprender el manejo y los factores de riesgo de mortalidad hospitalaria. en la Región Emilia-Romaña de Italia.

Específicos

- Conocer la relación entre comorbilidad e infecciones en pacientes de Medicina Interna.
- Evaluar los factores de riesgo de mortalidad hospitalaria.
- Conocer la utilidad de un índice de comorbilidad derivado de una modificación del índice de Elixhauser.
- Evaluar el impacto de los ingresos hospitalarios posteriores al trasplante renal en los servicios regionales italianos.
- Conocer los costes y el consumo de recursos, expresados por grupos de diagnosticos relacionados (GRD). Diagnósticos relacionados solo con hospitalizaciones de receptores de trasplante renal por todas las causas en la Región Emilia Romagna en Italia.

MATERIAL Y MÉTODOS

Estudio retrospectivo en la base de datos administrativa regional de la Región Emilia-Romaña de Italia.

La investigación sobre enfermedades infecciosas incluyó ingresos hospitalarios entre enero de 2013 y diciembre de 2016, registrados en la base de datos del hospital local. Se seleccionaron códigos administrativos para identificar infecciones, desarrollo de sepsis y calcular un puntaje de comorbilidad.

La segunda parte del trabajo evaluó todos los ingresos hospitalarios de receptores de trasplante renal entre 2001 y 2015. Calculamos el número de ingresos, la edad media, la duración de la estancia en el hospital, el valor medio de GRD y los costos de los ingresos durante el período de los 15 años estudiados.

RESULTADOS

En la primera parte del presente trabajo evaluamos más de 12.000 registros. Los sujetos fallecidos (n = 1545, 12,7%) eran mayores, tenían un mayor porcentaje de sepsis, infecciones pulmonares y endocarditis. El valor medio de la puntuación de comorbilidad también fue significativamente mayor. La sepsis, la endocarditis, las infecciones pulmonares y las infecciones del tracto urinario se asociaron independientemente con la mortalidad hospitalaria. Del mismo modo, el puntaje de comorbilidad (Odd Ratio – OR 1,070 por unidad de puntaje creciente), también se asoció independientemente con mortalidad intrahopitalaria (MIH). El riesgo ponderado calculado, obtenido al multiplicar 1.070 por el valor de puntaje promedio en pacientes fallecidos, fue de 19,367. Las áreas bajo la curva derivadas del análisis de las características operativas del receptor (ROC) relacionadas con la comorbilidad y el desarrollo de sepsis como predictores de mortalidad hospitalaria fueron 0,724 y 0,670, respectivamente. En la segunda parte del trabajo analizamos 9.197 receptores de trasplante renal ingresados en 15 años. La edad fue de 56,6 ± 1,6 años. Los ingresos fueron de 14,558, y la tasa media de receptores renales admitidos fue de 14.21 (* 100.000). La duración media y mediana de la estancia fue de 8,7 y 6 días, respectivamente. Los costos totales de las admisiones durante el período de estudio fueron de 72.717.232 € con valores medios de DRG de 3.409 €. El número de ingresos y el número total de días necesarios para los receptores de trasplante renal, así como la edad media de los pacientes ingresados, aumentaron de 2001 a 2015, sin embargo, la duración media y mediana de la estancia se mantuvo estable.

CONCLUSIONES

La evaluación cuidadosa de la comorbilidad es importante en los pacientes hospitalizados en las Unidades de Medicina Interna por enfermedades infecciosas, ya que la mortalidad hospitalaria está relacionada con la gravedad de la enfermedad y con la multimorbilidad. En estos pacientes, una evaluación cuidadosa de la comorbilidad debe representar un paso fundamental en el manejo de la enfermedad. La base de datos administrativa regional mostró que los costos relacionados con los ingresos de una población específica, como los receptores de trasplante renal, aumentaron gradualmente, probablemente debido al aumento del número de ingresos y al aumento de la edad. Mediante el uso de estas grandes bases de datos es posible evaluar un gran número de pacientes y diferentes entornos hospitalarios. Las bases de datos administrativas contienen información sobre demografía, tipo de hospital donde se realiza la atención, diagnóstico, procedimientos, duración de la estancia y estado al alta. Los investigadores podrían seleccionar condiciones y procedimientos específicos conociendo resultados complejos como la mortalidad. Aunque las bases de datos administrativas subestiman algunas enfermedades, se ha demostrado que son confiables con respecto a la comorbilidad. Es necesario tener en cuenta la comorbilidad para reducir la posible confusión en la investigación epidemiológica y las bases de datos administrativas permiten el desarrollo de nuevos índices de comorbilidad. En la primera parte del trabajo, se informó que la comorbilidad era un factor de riesgo de mortalidad hospitalaria en sujetos ingresados con enfermedades infecciosas. Indirectamente, también probamos un nuevo puntaje de comorbilidad. Finalmente, utilizamos la base de datos administrativa regional para probar una función peculiar de estos archivos. Evaluamos los costos de las hospitalizaciones por trasplante renal. Llegamos a la conclusión de que las bases de datos administrativas podrían utilizarse para la investigación de gestión clínica con diferentes objetivos.

PALABRAS CLAVE

Bases de datos administrativas, Comorbilidad, Puntaje de comorbilidad, Mortalidad hospitalaria, Ingresos, Costos, Enfermedades infecciosas, Receptores de trasplante renal, Gestión.

ABSTRACT

INTRODUCTION

Burden of comorbidities appears to be related to clinical outcomes in hospitalized patients and clinical stratification of admitted patients could be derived using administrative databases. The main aim of administrative data is obtained reimbursement, they are not planned for clinical research, therefore when they are used for clinical purposes, they should be carefully evaluated because subjects of interest could not be accurately defined. On the other hand administrative databases have several advantages such as population coverage, very large sample size, heterogeneity of covered population ("real-world" perspective), long observation periods, up to date information, no additional costs for gathering data, possibility to link several sources of information (e.g. hospitalizations, outpatient care, drug prescriptions, vital status). During the last decade, the research group from the Clinica Medina Unit (University Hospital Santa Anna, Ferrara) published several papers relating administrative databases to clinical conditions

OBJECTIVES

General

To evaluate the importance of comorbidities recoded during hospitalization in administrative databases in order to understand management and risk factors for in-hospital mortality in the Region Emilia-Romagna of Italy.

Specifics

- To know the relationship between comorbidity and infections in internal medicine patients.
- To evaluate risk factors for in-hospital mortality
- To test the usefulness of a comorbidity score derived from a modification of Elixhauser's index.
- To evaluate impact of hospital admissions subsequent to renal transplantation on Italian regional resources.
- To know costs and resource consuming, expressed by diagnosis related groups (DRG), related only to hospitalizations of renal transplant recipients for all causes in the Region Emilia Romagna in Italy.

MATERIAL AND METHODS

Retrospective study in the regional administrative database of the Region Emilia-Romagna of Italy. The investigation regarding infectious diseases included hospital admissions between January 2013, and December 2016, recorded in the database of the local hospital. Administrative codes were selected to identify infections, development of sepsis, and to calculate a comorbidity score. The second part of the work evaluated all hospital admissions of renal transplant recipients between 2001 and 2015. We calculated number of admissions, mean age, length of stay in the hospital, mean value of DRG and costs of admissions during the 15 year period of the study.

RESULTS

In the first half of this work we evaluated more than 12,000 records. Deceased subjects (n=1545, 12.7%) were older, had higher percentage of sepsis, pulmonary infections, and endocarditis. Mean value of comorbidity score was also significantly higher. Sepsis, endocarditis, pulmonary infections, and urinary tracts infections were independently associated with in-hospital mortality. In the same way, comorbidity score (OR 1.070 per unit of increasing score), was independently associated with IHM as well. The calculated weighted risk, obtained by multiplying 1.070 for the mean score value in deceased patients, was 19.367. The areas under the curve derived from receiver operating characteristic (ROC) analysis related to comorbidity and development of sepsis as predictors for in-hospital mortality were 0.724 and 0.670, respectively. In the second part of the work we analysed 9,197 renal transplant recipients admitted in 15 years. Age was 56.6±1.6 years. Admissions were 14,558, and mean rate of admitted renal recipients was 14.21(*100,000). Mean and median length of stay were 8.7 and 6 days, respectively. Total costs of admissions during the study period were € 72,717,232 with mean DRG values of € 3,409. Number of admissions and total number of days required for renal transplant recipients as well as mean age of admitted patients increased from 2001 to 2015, however mean and median length of stay remained stable.

CONCLUSIONS

Careful evaluation of comorbidity is important in internal medicine ward patients hospitalized for infectious disease, being in-hospital mortality related to severity of disease, and to multimorbidity. In these patients, a careful evaluation of comorbidity should represent a fundamental step in the disease management. Regional administrative database showed that costs related to admissions of a specific population such as renal transplant recipients gradually increased probably due to the increasing number of admissions and increasing age. By the use of these large databases it is possible to evaluate large number of patients and different hospital settings. Administrative databases contain information on demographic, type of hospital where care take place, diagnosis, procedures, length of stay and discharge status. Researchers could select specific conditions and procedures knowing hard outcomes such as mortality. Although administrative databases

underestimate some diseases, it has been shown that they are reliable regarding comorbidity. Comorbidity needs to be taken into account in order to reduce potential confounding in epidemiological research and administrative databases allow the development of new comorbidity indexes. Then in the first part of the work it was reported that comorbidity was a risk factor for in-hospital mortality in subjects admitted with infectious diseases. Indirectly, we also tested a new comorbidity score. Finally we used the regional administrative database for testing a function peculiar for these files. We evaluated costs of renal transplant hospitalizations. We conclude that administrative databases could be used for clinical management research aiming at different targets.

KEYWORDS: Administrative databases, comorbidity, comorbidity score, in-hospital mortality, admissions, costs, infectious diseases, renal transplant recipients, management

I. INTRODUCTION

1. CONCEPTUAL FRAMEWORK: Comorbidity. Administrative databases. Use of comorbidity indexes in clinical research

In western society multimorbidity and comorbidity have been recently recognized as a frequent condition causing increased complexity of managing diseases of both in-patients and out-patients. Prevalence of older subjects with different burden of organs dysfunction is increasing, however health systems are mainly organized for individual diseases treatment rather than multimorbidity management [Xu X et al 2017, Klompstra L et al 2019, Millà-Perseguer M et al 2019]. In the same way, in the great majority of cases, health care professionals` attitude is aimed at single diseases treatment. Causes of this change in epidemiology should be sought within technological advances and improvements in medical care and policy. Consequences of medical improvements is an increasingly number of patients surviving serious medical conditions that used to be fatal. As a result, and parallel to the aging of the population, a growing proportion of patients present with multiple coexisting medical conditions. It has been reported the distribution of multimorbidity, and of comorbidity of physical and mental health disorders, in relation to age and socioeconomic deprivation,

examining cross-sectionally 40 morbidities from a database of more than 1,700,000 people registered with 314 medical practices in Scotland [Barnett K et al 2012]. Authors found that 42.2% of all patients had one or more morbidities, and 23.2% were multimorbid. Subjects older than 65 years had higher prevalence of multimorbidity. Authors concluded that health care professionals should be supported in order to provide personalized, comprehensive continuity of care.

More than 50% of older adults have three or more chronic diseases and poor general conditions are associated with many adverse consequences, including death, disability, institutionalization, greater use of healthcare resources, poorer quality of life, and higher rates of adverse effects of treatment or interventions. It has been suggested that evidence-based clinical practice guidelines for single conditions, focusing on the management of a single disease could fail if treatment involves adults with multimorbidity [Barnett K et al 2012]. Evaluation of comorbidity is not easy and different methods have been suggested. Moreover, data to be taken into consideration for indexes calculation could derive from different sources [Lash TL et al 2007].

Observational studies dealing with epidemiology are designed aiming at acquiring data on sufficiently large and representative sample of subjects. Large database could be analyzed to provide meaningful, valid and generalizable results. Such a study requires considerable infrastructure including participants' recruitment, examination, follow-up and the storage of diagnoses or other study material [Vandenbroucke J et al 201]. Due to lack of resources scientific research, cost-effective alternatives of traditional observational studies are needed.

Administrative databases are massive warehouse of data collected in healthcare for different aims. Hospitals, health organisations and health insurance organisations manage such databases. Claims for reimbursement, records of health services, medical procedures, prescriptions and diagnoses information are stored in administrative databases, which provide a variety of already stored data with an on-going collection process [Yamana H et al 2015]. Moreover, they could provide an infrastructural basis for new data collection, which was not originally planned in the system, with minimal expenditure of resources.

Information stored in such databases was not planned for research purposes, administrative databases were originally thought as monitoring tools for health policymakers' management. Their primary use was to monitor healthcare systems' activity from an administrative and financial point of view. Therefore, administrative databases are different from other clinical data repositories, such as electronic health records, which are mainly used by clinicians to document patients' clinical conditions.

Administrative databases have been adopted as main approach of data source in different epidemiology-related fields such as pharmacoepidemiology. Pharmacoepidemiology records low-frequency or long-term adverse events due to drugs and vaccines, and requires high volume sample sizes, as well as long term follow-up periods. In this field, case-control or cohort designs are necessary. However, case-control studies in pharmacoepidemiology have been strongly criticised [Farrington CP et al 1996] due to selection and recall biases. Besides, case-control studies do not evaluate the absolute risk or the incidence of adverse outcomes in the population [Ehrenstein V 2010]. Analysis of administrative databases permits longitudinal design, incidence evaluation, large sample size and good power even for very rare events, associated with an inexpensive study design.

Also, large epidemiologic surveys and epidemiologic surveillance could detect significative results by using administrative databases. Cross-sectional studies or surveys calculate prevalence of risk factors and outcomes in the population. Surveys are often organized to investigate most prevalent health problems, with greater public interest such as obesity, smoking, education, violence [Margerison-Zilko C & Cubbin C 2013; Vozoris NT et al 2012; Comino EJ et al 2006; Cowling CS et al 2012]. Therefore resources could be difficult to justify for surveying outcomes and diseases with a low prevalence in the population. It should be underlined that self-report and non-participation influence survey results leading to information and selection bias. Another major point is that prevalence studies detect associations between epidemiologic factors and do not investigate causative relationships. Moreover, large surveys are not able to collect data from the same participants, and each time a different representative sample of the population is analysed, survey longitudinal perspective is not individual-based. The use of administrative databases provides a variety of clinical and personal data, with individual follow-up, and does not require the subjective involvement of study participants [Al Kazzi ES et al 2015].

Active surveillances are needed in the case of dynamically changing epidemiologic trends based on longitudinal data. Active ongoing data collection in prespecified time intervals are necessary, requiring considerable resource dedication and are usually undertaken for a selected group of specially prioritised epidemiologic issues. Infectious diseases' trends could be an example [Zhou W et al 2003; Falkenhorst G et al 2012; Simonsen J et al 2011; Iwane MK 2004; Bobo WV et al 2013]. Administrative databases can provide a suitable cost-effective alternative of these resource-demanding studies.

Administrative data evaluate quality of health-care and are provided by administering health service in order to plan reimbursement for health care service [Mues KE et al 2017]. Clinical physicians do not consider these data, arguing that information could not be trusted. However, several papers have been published, also by our group, analyzing administrative databases [Fabbian et al 2013 (a), 2013 (b), 2014; 2015 (a), 2015 (b), 2016 (a), 2016 (b), 2016 (c), 2016 (d), 2017, 2018 (a), 2018 (b), 2019 (a), 2019 (b), Fedeli 2017]. The latter usually include large populations and could evaluate sub-populations, are readily available, inexpensive, are easy to analyze with common statistical packages. By analyzing administrative databases patients' outcomes are available, determining patients benefit after health care interventions. Obviously, outcomes are not linked to specific medical practice. Comparing outcomes between different subpopulations often requires adjustment for patients' risk and the recognition that some subjects have worse clinical conditions than others. In today's environment comparison of administrative data from different countries could account for observed quality, and measuring quality across populations differ from quality for individual patients. Outcomes of populations probably depends from procedures and do not consider the single action of a single health care professional. From this point of view administrative data may assess quality of health care systems. Regional and central governments are the major managers and producers of administrative databases, at least in Europe. Although administrative databases are mainly dealing with information from acute care hospitals, information is increasing adding data from outpatients and long-term care. Being my work based on in-patients' care, my focus was on hospital discharge data set. In Italy administrative database contains clinical information based on the international classification of diseases, 9th revision, clinical modification (ICD-9-CM), and ICD-9-CM procedure codes.

Quality of administrative databases could be affected by clinical content (some diagnoses are missed), coding accuracy, completeness of coding, differences in data quality across hospitals and timing of events. Gaps in clinical information, questions about coding procedures, and the billing content could alter the quality of information. However, hospital discharge data set contain retrospective information, in fact diagnoses are assigned after discharge. Discharge diagnoses are related to conditions evaluated and treated at any time during the entire admission, regardless of when such conditions occurred. IHM is a hard outcome to consider, and it is never missed in administrative databases. In the majority of papers published by our group, IHM had been considered the dependent variable in the multivariate analysis, and it should be taken into account that administrative database could predict in-hospital mortality similarly to clinical findings at admission [Steen PM et al 1993; Iezzoni LI et al 1995 (a); Iezzoni LI et al 1995 (b); Iezzoni LI et al 1996 (a); Landon B et al 1996; Iezzoni LI et al 1996 (b)].

Typing the words "administrative data" in the search string of the search engine, Pubmed, it is possible to obtain more than 28,000 items. In 2018, the number of papers published dealing with administrative data was 2,868 a number higher than any previous year.

Healthcare providers collect a large amount of data commonly defined as healthcare administrative databases and providing a large variety of information including hospitalizations [Gavrielov-Yusim N & Friger M 2014]. Epidemiological, clinical and healthcare researchers keep on using administrative databases taking into consideration the advantages and disadvantages of them [Gavrielov-Yusim N & Friger M 2014; Nguyen LL & Barshes NR 2010; Grimes DA 2010]. Large sample size, population coverage and heterogeneity, which allow researchers to reflect the "real world" practice are considered advantages [Nguyen LL & Barshes NR 2010]. Moreover, researchers also appreciate absence of additional costs for gathering data, long observation periods, possibility of linking different databases and of performing trend analysis [Lipscombe LL & Hux JE 2007; Corrada E et al 2014]. Variable quality of collected data is the main disadvantage, Ioannidis underlined the importance of misclassification of different variables [Ioannidis IP 2013].

2. CONTEXTUAL FRAMEWORK

2.1. Italian National Health System

All following information are available at https://international.commonwealthfund.org/countries/italy/ (accessed 28/07/2019). The actual organization of the Italian National Health Service (Servizio Sanitario Nazionale) started in 1978, following the principles of universal coverage, solidarity, human dignity, and health needs. It is organized at a national, regional, and local levels. The central government controls the distribution of tax revenue for publicly financed health care and defines the “essential levels of care” (*livelli essenziali di assistenza,* or LEA) that could be offered to all residents in every region. The 19 regions and two autonomous provinces have the responsibility to organize and deliver health services through local health units. Regions enjoy significant autonomy in determining the macro structure of their health systems. Local health units general managers, decided by the governor of the region, manage primary care, hospital care, outpatient specialist care, public health care, and health care related to social care. The National Health Service (NHS) covers all citizens and legal foreign residents. Coverage is automatic and universal. Since 1998, undocumented immigrants have access to urgent and essential services. Temporary visitors receive health services by paying for the costs of treatment. The public system is financed primarily through a corporate tax (approximately 35.6% of the overall funding in 2012) pooled nationally and allocated back to regions, typically in proportion to their contributions, and a fixed proportion of national value-added tax revenue collected by the central government and redistributed to regions whose resources are insufficient to provide essential levels of care. The regions could generate their own additional revenue, leading to further interregional financing differences. Every year, the Standing Conference on Relations between the State, Regions, and Autonomous Provinces sets the criteria, based on population size and age demographics, to allocate funding to regions. Local health units are funded mainly through capitated budgets. Since the National Health Service does not allow people to opt out of the system and seek only private care, substitutive insurance does not exist, but complementary and supplementary private health insurance are available. Private health insurance plays a limited role in the health system. In 2010, around 5.5 percent of the population had individual voluntary health insurance coverage (1.33 million families), while around 2.5 million people had group coverage. Primary and inpatient care are free at the point of use. Medical necessity, effectiveness, human dignity, appropriateness, and efficiency in delivery are the criteria that identify services offered to all residents, including pharmaceuticals, inpatient care, preventive medicine, outpatient specialist care, home care, primary care, and hospice care. Regions can offer services not included at the essential levels of care but must finance them themselves. Prescription drugs are divided into three rank according to clinical effectiveness and, in part, cost-effectiveness. The first rank (*classe* A) includes lifesaving drugs and treatments for chronic conditions and is covered in all cases; the second (*classe* C) contains all other drugs and is not covered by the NHS. There is an additional rank (*classe* H) comprising drugs that can be delivered only in a hospital setting. The three tiers are updated regularly by the National Pharmaceutical Agency based on new clinical evidence. For some categories of drugs, therapeutic plans are mandated, and prescriptions must follow clinical guidelines. Procedures and specialist visits can be prescribed either by a general practitioner (GP) or by a specialist. While there are no user charges for GP consultations and hospital admission stays, patients pay a copayment for each prescribed procedure or specialist visit up to a ceiling determined by law. To reduce rising public debt, in July 2011 the government introduced, along with other economic initiatives, an additional copayment for each prescription. Copayments have also been applied to outpatient drugs at the regional level, and copayment has been introduced for "unnecessary" use of emergency services. Exemptions from cost-sharing are applied to people under age 6 and over age 65 who live in households with a gross income below a nationally defined threshold. People with severe disabilities, prisoners, are exempt from any cost-sharing. People with chronic or rare diseases, people who are HIV-positive, and pregnant women are exempt from cost-sharing for treatment related to their condition. Most screening services are provided free of charge. Primary care is provided by self-employed and independent physicians, general practitioners, and pediatricians, under contract and paid a capitation fee based on the number of people on their list. Local health units also can pay additional allowances for the delivery of planned care to specific patients, for reaching performance targets, or for delivering additional treatments. The payment levels, duties, and responsibilities of GPs are determined in a collective agreement signed every three years by consultation between central government and the GPs' trade unions. Regions and local health units can sign contracts covering additional services. In 2012, there were approximately 53,000 GPs and pediatricians and 104,600 hospital clinicians. Patients are required to register with a gatekeeping GP, who has incentives to prescribe and refer only as appropriate. People may choose any physician whose list has not reached the maximum number of patients allowed (1,500 for GPs and 800 for pediatricians) and may switch at any time. Legislation encourages GPs and pediatricians to work in three ways: base group practice, in which GPs from different offices share clinical experiences, develop guidelines, and participate in workshops that assess performance; network group practice, which functions like base group practice but allows GPs and pediatricians to access the same patient electronic health record system; and advanced group practice, in which GPs and pediatricians share the same office and patient health record system and are able to provide care to patients beyond individual catchment areas. Some regions are promoting care coordination by asking their GPs to work in groups comprising specialists, nurses, and social workers. The aim is for each group to be in charge of all the health needs of its assigned population. This arrangement is encouraged by additional payments to GPs per patient and by supplying teams with personnel. Outpatient specialist care is generally provided by local health units or by public and private accredited hospitals under contract with them. Once referred, patients are given a choice of any public or private accredited hospital but are not given a choice of specialist. Outpatient specialist visits are generally provided by self-employed specialists working under contract with the National Health Service. They are paid an hourly fee contracted nationally between the government and the trade unions. Outpatient specialists can see private patients without any limitations, whereas specialists employed by local health units and public hospitals cannot. Multispecialty groups are more common in northern regions of the country. Patient copayment is limited to outpatient specialist visits and diagnostic testing, while primary care visits are provided free of charge. In the case of after-hours emergency care, or when a consultation with a GP is not possible, service is provided by the emergency medical service (*guardia medica*), staffed by “continuous-care physicians” (*medici di continuità assistenziale*). The service normally operates at night and on weekends.

Depending on the region, public funds are allocated by local health units to public and accredited private hospitals. In 2012, there were approximately 187,000 beds in public hospitals and 45,500 in private accredited hospitals. Public hospitals either are managed directly by the local health units or operate as semi-independent public enterprises. A diagnosis-related group–based prospective payment system operates across the country and accounts for most hospital revenue but is generally not applied to hospitals run directly by local health units, where global budgets are common. Rates include all hospital costs, including those of physicians. Teaching hospitals receive additional payments (typically 8% to 10% of overall revenue) to cover extra costs related to teaching. Hospital-based physicians are salaried employees. Public-hospital physicians are prohibited from treating patients in private hospitals; all public physicians who see private patients in public hospitals pay a portion of their extra income to the hospital. Mental health care is provided by the National Health Service in a variety of community-based, publicly funded settings, including community mental health centers, community psychiatric diagnostic centers, general hospital inpatient wards, and residential and semiresidential facilities. In 2012, there were 1,938 residential facilities and 819 semiresidential facilities, providing care to approximately 69,000 patients. The promotion and coordination of mental illness prevention, care, and rehabilitation are the responsibility of specific mental health departments in local health units. These are based on a multidisciplinary team, including psychiatrists, psychologists, nurses, social workers, educators, occupational therapists, people with training in psychosocial rehabilitation, and secretarial staff. In most cases, primary care does not play a role in the provision of mental health care. Patients who need long-term care and social supports are generally treated in residential (approximately 180,000 beds in 2012) or semiresidential (14,000 beds) facilities or in home care (approximately 634,000 cases). Residential and semiresidential services provide nurses, physicians, specialist care, rehabilitation services, medical therapies, and devices. Patients must be referred to receive residential care. Cost-sharing for residential services varies widely according to region but is generally determined by patients' income. Community home care is funded publicly, whereas residential facilities are managed by a mixture of public and private, for-profit and nonprofit organizations. Community home care is designed not to provide physical or mental care services but to provide additional assistance during a treatment or therapy. In spite of government provision of residential and home care services, long-term care in Italy has traditionally been characterized by a low degree of public financing and provision as compared with other European countries. Accompanying allowance: Awarded by the National Pension Institute to all Italian citizens who need continuous assistance. The allowance, which is related to need but not to income or age, amounts to approximately EUR500 per month. Care vouchers are awarded by municipalities on the basis of income, need, and clinical severity only to residents of those municipalities offering the service. Voluntary organizations still play a crucial role in the delivery of palliative care. A national policy on palliative care has been in place since the late 1990s and has contributed to an increase in services such as hospices, day care centers, and palliative care units within hospitals. In 2012, there were 176 hospices, with approximately 1,800 beds. But much still needs to be done to ensure the diffusion of palliative care services because disparities persist: northern regions cared, on average, for 54 patients per 100,000 residents, while in central and southern regions the rate fell to 27 patients. Government at both the national and regional levels are responsible for upholding quality and ensuring that services included in the essential levels of care are provided and that waiting times are monitored. Several regions have introduced programs for prioritizing delivery of care on the basis of clinical appropriateness of services prescribed and patient severity. All doctors under contract with the National Health Service must be certified, and all National Health Service staff participate in compulsory continuing education. The National Commission for Accreditation and Quality of Care is responsible for outlining the criteria used to select providers and for evaluating regional accreditation models (including private hospitals), which vary considerably across the system. These models do not usually include periodic reaccreditation. National legislation requires all public health care providers to issue a "health service chart" with information on service performance, quality indicators, waiting times, quality assurance strategies, and the process for patient complaints. These charts have also been adopted by the private sector for its accreditation process and must be published annually, although dissemination methods are decided regionally. Most providers disseminate data through leaflets and the Internet. The National Plan for Clinical Guidelines (Piano Nazionale Linee Guida) has been implemented in recent years and has produced guidelines on topics ranging from cardiology to cancer prevention and from appropriate use of antibiotics to cesarean delivery. Integration of health and social care services has recently improved, with a significant shift of long-term care from institutions to the communities and an emphasis on home care. Community home care establishes a home care network that integrates the competencies of nurses, GPs, and specialist physicians with the needs and involvement of the family. GPs oversee the home care network, cooperate with social workers and other sectors of care, and take responsibility for patient outcomes. The regions have chronic care management programs, dealing mainly with high-prevalence conditions such as diabetes, congestive heart failure, and respiratory conditions. All programs involve different competencies. Some regions are also trying to set up disease management programs based on the chronic care model, although the degree of organization varies across regions. The New Health Information System (*Nuovo Sistema Informativo Sanitario*) has been implemented incrementally since 2002, with the goal of establishing a universal system of electronic records connecting every level of care. It provides information on services, resource use, and costs, but does not encompass all areas of health care; in particular, primary care is not included, while hospital, emergency, outpatient specialist, residential, and palliative care, as well as pharmaceuticals, are. It currently registers administrative information on care delivered, but medical information appears to be more difficult to gather. No unique patient identifier exists at the national level. Some regions have developed computerized networks to facilitate communication between physicians, pediatricians, hospitals, and territorial services and to improve continuity of care. These networks allow the automatic transfer of patient registers and of information on services provided, prescriptions for specialist visits and diagnostics, and laboratory and radiology test outcomes. A few regions have also developed a personal electronic health record, accessible by the patient, that contains all his or her medical information, such as outpatient specialty care results, medical prescriptions, and hospital discharge instructions. Personal electronic health records are meant to provide support to patients and clinicians across the whole process of care, but diffusion is still limited. Containing health care costs is a core concern of the central government, as Italy's public debt is among the highest of the industrialized nations. Fiscal capacity varies greatly across regions. To meet cost-containment objectives, the central government can impose recovery plans on regions with health care expenditure deficits. These identify tools and measures needed to achieve economic balance: revision of hospital and diagnostic fees, reduction of the number of beds, increased copayments for pharmaceuticals, and reduction of human resources through limited turnover. Because of the regionalization of the health system, most innovations in the delivery of care take place at the regional rather than the national level, with some regions viewed as leaders in innovation. In April 2015, the Ministry of Health approved a decree for the reorganization of hospital care. The decree classifies public hospitals into three groups:

Base hospitals (for populations of 80,000–150,000 residents), with emergency wards, internal medicine, general surgery, orthopedics, and on-call availability of radiology, laboratory testing, and blood bank.

First-level hospitals (150,000–300,000 residents), with the same wards as base hospitals and, in addition: obstetrics (based on the number of deliveries per year), pediatrics, cardiology with intensive care unit, neurology, psychiatrics, oncology, ophthalmology, otolaryngology, and urology.

Second-level hospitals (600,000–1,200,000 residents), with advanced emergency wards and facilities for treating highly complex patients (or conditions).

In addition, the decree introduces, for a few procedures, minimum levels of activity and quality thresholds.

2.2. Health care at University Hospital St. Anna in Ferrara

University Hospital St. Anna Hospital is a 626-bed teaching hospital with all facilities, excluding only cardiothoracic surgery. The majority of admissions derive from the province of Ferrara, in which the hospital serves as the hub centre. The province of Ferrara (≈ 350,000 inhabitants, mean age 47.3 years) is served by one Teaching Hospital (hub centre) and three community hospitals (spoke centres, ≈ 200 beds/each). Local economy is mainly agriculture-based, and in minor part industrial. The annual flow of patients by the emergency department (ED) is approximately 90,000, mainly elderly subjects due to the fact that the area is characterized by a high percentage of elderly subjects (26 % are older than 65 years), and approximately 3000 subjects are aged more than 90 years. The Department of Medicine consists of four Internal Medicine units, two Infectious Disease units, and one each of Geriatrics, and Gastroenterology (165 total beds, 24/24 h and 7/7 days open to the ED admissions). About one-third of all hospital admissions are directed to the Department of Medicine. The great part of medical and nursing staff is permanent, covering also festive days or holidays.

2.3. General characteristics of administrative databases

The main aim of administrative data is obtained reimbursement, they are not planned for clinical research, therefore when they are used for clinical purposes, they should be carefully used because subjects of interest could not be accurately defined. The latter is especially true for chronic conditions usually managed on an outpatient basis [Nguyen LL & Barshes NR 2010; Grimes DA 2010]. However, researchers know which information can be used and which should be excluded from the analysis [Van Walraven C & Austin P 2012]. Research groups usually include experts of the particular data set, experts of coding rules, clinicians and statisticians. Depending on the country, and type of healthcare system the population covered by administrative databases could be different, however, in Europe the total resident population is represented. Reduced sampling errors due to large sample size and heterogeneity of the population allow to represent "real world" practice [Nguyen LL & Barshes NR 2010]. A careful description of database characteristics is really important in order to clarify the aim of the study [Van Walraven C & Austin P 2012].

2.3.1. Limitations of Italian administrative databases

Biases found in administrative data research might be classified as belonging to either information or selection bias family. Information bias occurs if data collection is imperfect, and is mainly signified in misclassification or outcome [Available at: whqlibdoc.who.int/hq/2011/WHO_HSE_GIP_2011.1_eng.pdf (accessed 28/07/2019)].

The condition (disease under investigation) documented in patients' records should be correctly defined. Misclassification of the outcome may be a result of erroneous or unclear clinical documentation as well as a result of misdiagnosis. Also exposure misclassifications, as well as, misclassified use of medication, have been previously reported [Greenfield G et al 2012]. Medication could be improperly reported in administrative databases, especially if drug purchase is not reimbursed [Gamble JM et al 2012]. Another issue in pharmaceutical exposure is treatment adherence and compliance, pharmaceutical databases provide information regarding whether a patient received a drug prescription, but information about ingestion of the drug and in what dosage is lacking [Gamble JM et al 2012].

Information bias could depend on the type of healthcare systems existing in a country, especially using administrative databases in countries with coexisting universal public and private healthcare systems. In such a case, measurement of visits number could be erroneous. Administrative databases are not designed for research, the quality of information depends greatly on specific incentives of data reporting, information in administrative databases is most accurately represented when it has important administrative or financial implications. As a result, expensive medical procedures are documented better than less costly, but nonetheless clinically important, health interventions.

Clinical guidelines and definitions may change, as well as the clinical coding system, in fact the coding system may be transformed with time. Another type of information bias is called "immortal time bias" [Suissa S 2008]. This bias occurs because an esatblished initial interval of the follow-up period is erroneously classified as exposed while in fact being unexposed. Therefore, this interval called immortal time, adds guaranteed protected survival time to the exposed group and systematically distorts causal associations. This bias inflates the survival of the treated group and overestimates the protective effect of treatment [Fiscella K & Fremont AM 2006]. Immortal bias can be avoided by carefully defining the follow-up period during data retrieval from the database. Specifically, the definition of index time for the exposed and unexposed cohorts must be equivalent [Virani SS et al 2013]. Cox proportional hazard should be used, where the exposure is modelled in a time-dependent manner.

Area-level data, also defined aggregate data, are personal information collected in administrative databases. Patients' privacy is the main reason for providing them in aggregated form. Area-level data is applied for data of personal character, such as income, race and ethnicity [Available at: www.ahrq.gov/research/findings/final-reports/medicareindicators/medicareindicators.pdf] (accessed 22/08/2019)]. Patients' socioeconomic status (SES) may be derived from the general socio-demographic composition of their area of residence, and this method of data imputation is defined 'geocoding' [Available at: www.ahrq.gov/research/findings/final-reports/medicareindicators/medicareindicators.pdf (accessed 22/08/2019)]. Geocoding is used to link the list of patients and their addresses, derived from the administrative database, with census-derived information, such as rates of poverty, levels of education and employment, ethnic and racial composition, on geographically defined areas of residence [Greenland S & Robins J 1994]. In the analysis of area-level data it is important to use a multilevel analytical approach, such as multilevel or hierarchical modelling [Diez Roux AV 2002]. Administrative databases provide different type of information, therefore, for a correct modelling, it is important to differentiate between the group and individual sources of variability. Models that combine individual and grouping variables, should be built using a multilevel approach.

The most frequent criticism made against administrative data is about generalizability, also defined as external validity of study results. Results, in order to be considered credible and meaningful, should involve large geographically distributed populations. Optimizing internal validity, the results of the analysis will be applicable to different populations. When researchers are conscious of the features defining the database population, interpretation of findings would be easy without difficulties.

Health administrative data are frequently used in order to evaluate health research and analysis of these data has been facilitated by the use of a standard system for coding diagnoses. This type of research is related to data quality and validity limitations, which arise because the data are not created for research purposes. Some conditions could not be properly coded, raising concern for research organizations that were left without a valid means of properly coding or even identifying new or varied diseases and medical technologies. It is imperative that researchers have access to accurate and comprehensive data when tracking potential global epidemics, pandemics and deadly outbreaks. Keeping updating coding provides important details that enable early and better identification of therapeutic outcomes.

For clinical research an up-to-date coding system is expected to lead to better information gathering on comorbidities and serious adverse events. ICD-9-CM and 10th Revision of ICD-10-CM are the most universally applied classification systems for coding diagnoses, reasons for healthcare utilization, health status, and external causes of injury. In Italy, it has been using ICD-9-CM, even if the current ICD-9-CM diagnosis codes do not provide sufficient clinical specificity to describe the severity or complexity of the various disease conditions. The current ICD-9-CM system is ineffective for effectively monitoring utilization of resources, measuring performance, and analyzing healthcare costs and outcomes. Historically, ICD-9-CM was developed as a classification system for statistical compilation of data in inpatient settings. In 1994, WHO developed the 10th revision of the ICD system. The purpose of the revision was to expand the content, purpose, and scope of the system and to include ambulatory care services, increase clinical detail, capture risk factors in primary care, include emergent diseases, and group diagnoses for epidemiological purposes.

In 1997, the National Center for Health Statistics began the first round of testing following the development of ICD-10-CM. A timetable for the implementation of ICD-10-CM has not been determined. Many of the problems with ICD-9-CM have been addressed in ICD-10-CM. It provides better information for non-acute care or nonhospital utilization, clinical decision making, and outcomes research. Terminology and disease classification have been updated to be consistent with current usage and medical advances.

Significant improvements in both the content and the format of ICD-10-CM include the following:

- ICD-10-CM codes are alphanumeric and include all letters except "U," thus providing a greater pool of code numbers.
- ICD-9-CM’s V and E codes are incorporated into the main classification in ICD-10-CM.

- The length of codes in ICD-10-CM can be a maximum of seven characters (digits and letters) as opposed to ICD-9-CM's five digits.
- ICD-10-CM offers the addition of information relative to ambulatory and managed care utilization.
- Conditions that are new or that were not uniquely identified in ICD-9-CM have been assigned code numbers in ICD-10-CM.
- In ICD-10-CM, some three-character categories are not used in order to allow for revisions and future expansion.
- Instead of grouping by categories of injury or type of wound, ICD-10-CM groups injuries by site of the injury and then the type.
- A guidance on the hierarchy of the chapters and to clarify priority of code assignment has been added.
- Some conditions with a new treatment protocol or perhaps a recently discovered or new etiology have been listed in a more appropriate chapter.
- Combination codes are used for both symptom and diagnosis, and etiology and manifestations.
- Codes for postoperative complications have been expanded. Also, a distinction has been made between intraoperative complications and post-procedural disorders.

Table 1. *Advantages and disadvantages in the use of administrative data (Suissa S & Garbe E 2007, Wild S et al 2016)*

Advantages	**Disadvantages**
Population coverage	Expertise on the specific database is needed to ensure the correct use of data
Very large sample size	Not planned for health research, they lack of specific clinical information
Heterogeneity of covered population ("real-world" perspective)	Quality of data is affected by their administrative use, e.g. for reimbursement
Long observation periods	Case selection based on diagnosis codes; validation studies are needed
Up to date information	Possible misclassification of outcomes or exposure
No additional costs for gathering data	Difficulties to control confounding factors and to draw causal relations
Possibility to link several sources of information (e.g. hospitalizations, outpatient care, drug prescriptions, vital status)	Statistical significance is easily achieved; clinical relevance has to be taken into account in statistical analysis and in discussing results

Table 2. *How to read a work based on administrative data*

Criteria	Yes	No
Information based on administrative data should be checked		
Target population should be clearly stated		
Characteristics of the underlying health care system should be reported		
Variables derived from the administrative database should be stated		
Correct definition of criteria selection		
Previous paper using similar design should be discussed		
Evaluation of comorbidity should be reported		
Statistical modeling should be stated		

Note: *Self-made elaboration table*

2.4. Issues that need to be taken into consideration in studies using administrative databases

2.4.1. Data quality

The first steps in the analysis of administrative databases should be checking completeness (rate of missing values), correctness (invalid data, out of range data, outliers), agreement between fields, and temporal consistency. In order to protect privacy, a data set identifier is assigned to each patient, and this number replaces the usual identifier that is commonly used. The inability to identify a record could lead to the exclusion of a specific case from the analysis. Therefore, the number of records with missing identification number should be evaluated. [Mazzali C et al 2015].

2.4.2. Case selection

Selection of subjects affected by a specific disease is performed on the basis of ICD-9-CM and ICD-10-CM depending on the country. Disease classification systems is used to code illness managed during a hospital stay in discharge abstracts. Researchers define groups of patients with a defined disease by using these disease codes and their position in the discharge abstract, usually these codes depending on their position in the discharge abstract define primary and secondary diagnoses. The association between the codes and the real disease that is documented in the health records is evaluated by studies that calculate sensitivity (SE), specificity (SP) and positive predictive value (PPV) related to a specific code [Saczynski JS et al 2012].

2.4.3. Comorbidities

In clinical studies analyzing administrative database, it is critical to take into account patients' comorbidities. In order to control for comorbidities in administrative database, several measures have been proposed, comorbidity scores have become increasingly popular because they are easy to calculate and widely accepted [Gagne JJ et al 2011; Schneeweiss S et al 2003]. Secondary diagnoses reported in hospital discharge abstracts are necessary in order to identify comorbidities and calculate comorbidity index or score. Different comorbidity scores have been published in medical literature for medical, surgical, intensive care unit, pediatric and geriatric patients, some derived from clinical data and others derived from administrative data. Comorbidity scores are better able to predict long-term mortality than short-term mortality, inpatient mortality or any mortality within 30 days from admission [Sharabiani MTA et al 2012]. Charlson index [Romano PS et al 1993] and Elixhauser index [Elixhauser A et al 1998] are the two scores with the higher number of studies and show to be good predictors of long-term mortality. Moreover, it has to be considered that comorbidities could be under-reported in patients with severe acute conditions. The accuracy and completeness of the data are essential in order to calculate effective comorbidity score; low quality data could reduce the performance of a comorbidity score and its ability to predict the outcome of the study [Schneeweiss S et al 2003].

2.4.4. Statistical analysis

Administrative databases have been analyzed in the same way as observational studies have been evaluated. However, administrative databases usually contain very large sample size and data are usually clustered in order to evaluate a limited sample.

Due to the large amount of data the associations between outcome variables and exposures or patient characteristics are quite easily statistically significant, and sometime the clinical significance could be negligible. Usually diseases that commonly affect the population and that could be easily diagnosed by physicians are analyzed in order reduce bias selection.

The analysis of administrative database could only show independent association, while the causal relationship between exposure factors and outcomes is difficult to prove due to confounding events and bias. A control group could be enrolled to detect confounding events or bias in these observational studies [Lipsitich M et al 2010]

In population-based epidemiological studies administrative databases allow population-based studies to evaluate incidence, prevalence, and temporal trends of specific diseases, health conditions and the associated mortality. Population-based studies could be important instruments for policy makers to consider when planning public interventions.

One of the most important outcome that could be investigated using administrative database includes mortality, both in terms of short- and long-term mortality, but also hospital readmission and length of stay in the hospital. Such outcomes are easily calculated from administrative databases.

Administrative databases analysis suggests the effect of demographic characteristics such as sex, age, race and major medical conditions on outcomes without a previous selection of patients, but considering subjects encountered in everyday clinical practice.

Also, socioeconomic status could be taken into account and could be related to development of different diseases. Indicators of residents' socioeconomic status are usually evaluated by institutions for social research. The evaluation of the effects of socioeconomic status on outcomes could be useful in studying the effectiveness of primary and secondary prevention [Jong P et al 2002].

Also, quality of care, inequalities of outcomes and treatments and their trends, the association between hospital volume and processes and outcomes, and avoidable hospitalizations are frequent topics in studies involving administrative databases [Sinha S et al 2012].

A different item related to quality of care and the use of administrative databases is the comparison of the performance of hospitals, such as teaching vs. non-teaching hospitals. [Dehmer GJ et al 2014].

However, comorbidity calculated using administrative databases could affect comparison between hospitals, in fact misclassification of important covariates in different groups cannot be excluded, due to comorbidities coding [Ioannidis IP 2013]. Moreover, several clinical confounders are not recorded, and cannot be accounted for in the models, such as weight and smoking status.

Administrative databases could improve knowledge found in randomized clinical trials; however, careful attention must be put into the design, case selection, and analysis of studies. Detection codes need to be validated. Finally, the cause–effect relationship of statistical associations with "statistically significant" predictive factors has to be deeply considered, discussed and understood.

2.5. Impact of administrative database studies in clinical knowledge

The number of papers published reporting results based on administrative databases analysis have been increasing in recent years, and advantages and disadvantages of such a type of studies need to be carefully considered. Administrative databases allow population-based studies evaluating changes and trends of outcomes over time, and observe the effects of applied medical and nursing treatments from a "real-world" perspective. However, they rely on coded diagnoses to select population of interest, and this action could result in selection bias. Finally, due to lack of clinical information, it is difficult to adjust for all confounding factors when comparison between different groups is performed. In order to ensure the correct use, an in-depth understanding of the underlying healthcare and data registration and coding systems, an interdisciplinary collaboration of clinicians, coding experts, epidemiologists, and statisticians is necessary. The population should be accurately described considering the reported selection strategy, the eligibility criteria, and the comorbidity index calculated. In the future, the increasing availability of routinely collected data will offer more information that would be analyzed. Electronic healthcare records are available in different healthcare systems and represent a comprehensive set of information that could be linked to administrative databases.

2.6. Evaluation of comorbidity by indexes

Conditions that coexist with a disease of interest are defined comorbidities. Delay in effective diagnosis and treatment decisions, reduced survival, and confounding analysis have been ascribed to comorbid illnesses. Nowadays clinical researches need to measure comorbidity, however methods for such an evaluation could demonstrate relative strengths and weaknesses. Selection of an effective index for a specific study it is important in order to provide a right methodology to organize, summarize, and compare results, therefore choosing a good index with right properties could increase quality of results.

2.7. Reason for measuring comorbidity

The index illness and comorbidities influence patients' treatment, moreover age, institutional beliefs, personal preference, socioeconomic conditions and education should be taken into consideration. Kaplan and Feinstein stated, ''In clinical practice, the prognostic influences of age and comorbidity are well recognized, and these influences usually receive careful consideration during the diverse decisions of clinical judgment. In statistical studies, the effects of comorbidity are generally ignored'' [Kaplan MH & Feinstein AR 1974]. At the time of subjects' selection in a clinical study, in order to consider if selection bias exists, they need to be stratified by risk for statistical analysis, and a valid measurement of comorbid illness is essential for comparison. Gijsen et al. [Gijsen R et al 2001] and Greenfield et al. [Greenfield S et al 1988] reviewed causes and consequences of comorbidity, especially considering the impact of comorbidity on survival [Hall SF et al 2000; Piccirillo JF et al 2004].

2.8. Comorbidity scores

Comorbidity is related to any other or coexistent conditions different from the index illness. All relevant diseases, disorders, or conditions excluding the index disease could alter the prognosis. Past history, organs abnormalities, and the list of current medications are normally investigated in everyday clinical practice. Considering a clinical study comorbidity usually includes heart disease, chronic obstructive pulmonary disease, diabetes mellitus, cerebral diseases, renal dysfunction and pulmonary embolus. A comorbidity index summarizes all the coexistent illnesses to a single numeric score, allowing comparison with scores from other patients. The index suggests the severity of a patient's medical history, and a single patient may present different scores, depending on the disease of interest. Comorbidity is different from multimorbidity, multimorbidity represents the coexistence of >2 illnesses in the same patient without considering any index disease [Gijsen R et al 2001]. However, if we aim to assess the impact of all illnesses on the overall health of a patient, the use of a comorbidity score could not be correct. In these cases, physicians should use performance scales (such as the Karnofsky or Eastern Cooperative Oncology Group [ECOG]) or functional assessment scales (such as the Activities of Daily Living [ADL]).

2.8.1. Timing for using a comorbidity index

Retrospective or prospective observational studies need to stratify patients into groups with similar risk, therefore clinical researchers use a comorbidity index. However, clinical judgment is still the best way in order to make the right decision for a specific patient.

2.8.2. Purpose and origin

Specific needs push researchers to design clinical studies differently, and therefore it is important for an investigator to understand the reasons and setting of the index that were considered at the time of its development. The Cumulative Illness Rating Scale (CIRS) was developed taking into consideration IHM of a series of men a southeastern United State (US) veterans hospital in 1964. The CIRS was designed to ‘‘estimate total medical burden and capacity for elderly patients to survive’’ and was not developed as a comorbidity index [Linn BS et al 1968]. Subsequently, by removing the disease of interest, CIRS has been converted to a comorbidity index. The Kaplan-Feinstein Classification (KFC) was designed to demonstrate that "comorbidity was a crucial and confounding variable" and was based on 188 newly diagnosed diabetic male patients followed in an outpatient clinic at the New Haven Veteran's Hospital between 1959 and 1962 [Kaplan MH & Feinstein AR 1974]. The Charlson Comorbidity Index (CCI) is a ‘‘taxonomy for comorbid conditions that might alter short term mortality’’ and was designed based on the mortality of 607 patients admitted to a general internal medicine service in a single New England hospital during 1 month in 1984 [Charlson ME et al 1987]. The Index of Coexistent disease (ICED) was created to demonstrate that ‘‘illness due to diseases other than the primary illness may affect the outcome of interest over the period of observation’’ [Cleary PD et al 1991]. Clinical researches should compare their study design with the original study population of the index.

2.8.3. General data

Comorbidity indices are multi-item predictive indices with three components: items, a severity scale (including criteria), and a scoring system. The ICED, has 27 items, the CIRS and the CCI are summarizing scores, and the KFC and the ICED are ordinal, using the greatest single scores. Ranges of the scores are very different, as well as the items considered for their calculation. Consideration of the variables needed for score calculation are important factors in choosing an index.

2.8.4. Content validity

Both completeness and relevance of the content of the items to measuring what they claim to measure define content validity. Content validity is a reflection of the development of a score. Parameters and severity scale appropriately describe the phenomenon of comorbidity by content validity, however it could be that any irrelevant items are included. Content validity is related to the original design and to any modifications of original criteria. CIRS, KFC, and ICED were made up by the authors solely based on clinical experience, and CCI was developed using a statistical methodology for item generation and reduction. The parameters in all four indices probably describe the wide range of comorbid conditions, however some exceptions could or could not be relevant to a planned study. ICED includes only cerebral vascular disease and has no psychiatric items. The CIRS and the KFC consider alcoholism using severity scores under the hepatobiliary item, but with the ICED and the CCI alcoholism per se does not appear and the patient would score positive only if known to have a liver disease. Moreover, the categories of the severity scales within the items could not describe the possible range of conditions. Timing of criteria and upgrades may be important in assessing content validity. The criteria for the CIRS, KFC, and CCI are based on medical knowledge and treatments from more than 20 years ago. Different scores have been substantially upgraded [Hall SF et al 2000; Piccirillo JF et al 2004].

2.8.5. Face validity

The sensibility of the measurement based on the experienced common sense of clinical researchers define face validity. How the index works, and whether it works in a study should be considered. Some indexes assume that all the parameters and the severity categories have the same relative impact on the patient’s health (also called internal validity). The CIRS assumes that the impact of all diseases is additive and the KFC assumes that the single most severe illness will determine the prognosis (the KFC also scores a patient with two moderately severe illnesses as ‘severe,’ assuming some additive effect). The ICED allows a high score in functional status severity to override a high disease severity score. The different assumptions on the different scoring systems have been hardly tested or confirmed and superiority of a score over the others is still a matter of debate.

2.8.6. Reliability

'The extent to which repeated measurements of a stable phenomenon by different people, at different times and places get similar results'' defines reliability [Fletcher RH et al 1996]. Clinical researches would not use a score that is not reliable in a specific research setting, even if content and face validity are considered important.

Data abstraction process by abstractors that is then used to calculate scores, defines interrater reliability (IRR). Clarity of criteria and ease of use are related to reliability of the IRR, however also different factors such as record quality, training of abstractors, background education of abstractors and experience of abstractors should be considered.

2.8.7. Predictive ability

Criterion and construct validity should be assessed however they are hardly known by clinicians. The term construct validity needs to be related to scale performance under different conditions, such as with different groups of patients or before and after treatment. Moreover, comparison of the performance of a score with a different one considered as gold standard in a similar study design defines criterion validity. Concurrent and predictive define the two subtypes of criterion validity. Conwell et al. [Conwell Y et al 1993] evaluated concurrent criterion validity comparing results of the CIRS based on chart review to the CIRS based on autopsy findings in the same population. Papers, evaluating scores measuring comorbid illness, successfully stratified patients by an outcome, and they could be interpreted as comorbidity indices created as predictive indices. As a consequence, several publications could be evaluated as examples of predictive criterion validity.

Taking into consideration the most important papers published on this item it is possible to understand that geriatric and psychiatric literature used mainly CIRS, oncology papers evaluated KFC, and health policy and renal disease ICED. On the other hand, CCI is frequently used, due to the fact, that it has been evaluated in different clinical setting.

2.8.8. Feasibility

Simplicity, ease of use, training requirements, availability of a manual and time of administration define feasibility. All indices require significant training to be correctly used [Waite K et al 1994].

2.8.9. Generalizability

Results from different studies calculating and testing scores in different populations in different clinical settings suggest the problem of generalizability of results. Researchers need to discuss whether the results from the test study population, subsequent validation studies and results from their own study population, would be confrontable.

2.8.10. Indications for researchers

Researchers would choose the comorbidity index according to the proposed setting and experience based on the relative validity of each of the indices [Cleary PD et al 1991]. In case of content validity, probably the CCI and the CIRS are better due to higher statistical methodology. In case of face validity, the CIRS is better due to the fact that it is a summative scale of all items. The CCI is the most commonly used index, however, it is hard to imagine that the 16 identified and explicit causes of 1 year mortality of 604 general medical admissions in one month during 1981 can have specific applications more than 2 decades later. In order to choose the right index, it is necessary to analyze type and completeness of information, quality of records, the detail of patient data available, because they need to be matched. The CIRS and CCI create continuous variables, whilst KFC and ICED produce an ordinal variable, therefore researchers need to analyze which type would be most appropriate for the planned statistical analysis of the data.

Type of distribution of different scores could be important for study design, CIRS suggests a normal distribution, KFC divides population in four similar groups of patients, using CCI most patients score zero and the number of 'sickest' patients is low. Finally, researchers should know that due to differences in items, severity scales and scoring, different indices for the same patient or patients may score differently and that different indices identify different patients as the 'sickest.' There are many site-specific indices available, such as specific indices for particular settings, usually they are created by modifying existing indices or created from specific datasets

Clinical epidemiology has been reported to be ''the study of the variation in the outcome of illness and of the reasons for that variation'' [Weiss NS 1986]. However, it is important to understand treatment and outcome variation in different period of time, and outcome needs to be compared in subjects with similar comorbidity.

2.9. Charlson Comorbidity Index (CCI)

The CCI appeared in the international literature in 1987, and was based on the mortality rates of patients admitted to the general internal medicine service (APPENDIX II).

The aim of that study was to develop a method that could prospectively classify comorbidities able to alter the risk of mortality. Sixteen diseases were included, with different weights, and were selected and weighted based on the strength of their association with mortality.

By the use of clinical data items and their weights included in the CCI were statistically derived by the relative risk estimates of the proportional regression model to predict mortality, considering that items were explicit and mutually exclusive. Not all comorbidities were considered, for example alcoholism was excluded [Kaplan MH & Feinstein AR 1974]. However different conditions could not be included. Charlson comorbidity index (CCI) has been adapted for ICD-9-CM database [Charlson ME et al 1994; Schneeweiss S & Maclure M 2000; Deyo RA et al 1992].

2.10. Elixausher Comorbidity Index (EI)

Elixhauser et al. [Elixhauser et al. 1998] used administrative data to identify the 30 comorbidities that had a major impact on short-term out comes in admitted patients for acute conditions counting them separately. EI included a higher number of items compared to the CCI, however no weight was attributed to each comorbidity, implicitly assuming that all conditions were equally important in their impact on outcomes (APPENDIX III).

When EI was compared to CCI, EI tended to outperform CCI [Condon JR et al 2012; Southern DA et al 2004; Menendez ME et al 2014; Dominick KL et al 2005], however it has also been reported similar performances [Antoniou T et al 2014].

2.11. Comparison of Charlson Comorbidity and Elixhauser Index

An illness or more illnesses coexisting with an index disease of interest define comorbidity. Comorbidities may delay diagnosis, may confound clinical analysis and importantly, could impact mortality. Comorbidity has been found to be a significant predictor of negative outcome, therefore, due to the aging of the worldwide population, it is important to evaluate it efficiently.

In clinical practice, the two well-known methods that summarize comorbidity are CCI and EI: both collecting each disease separately or summarising comorbidity into an index providing a single parameter for measuring such an important parameter [Charlson ME et al 1987] [Elixhauser A et al 1998].

Comparison of comorbidity between patients is an advantage due to the fact that reducing all coexistent illnesses and the severity into a single numeric score, make possible comparison between populations.

3. BACKGROUND

3.1. Papers published in which administrative databases were used for clinical purposes

In the last decade, our research group published a significant number pf papers using administrative databases for clinical purpose. Analysis of hospitalizations was conducted at different level geographical levels.

3.1.1. Hospitalizations at University Hospital St. Anna in Ferrara

The studies conducted with the approval of the local institutional committees for human research, included all hospital admissions for different causes during an established period of time, recorded in the database of the University Hospital St. Anna of Ferrara, Region Emilia-Romagna (RER) of Italy, and maintained by the Centre for Health Statistics. Since 1999, the University Hospital St. Anna of Ferrara started to use an electronic database to store all the discharge hospital records (DHR) of hospitalized patient; these DHR report, gender, date of birth, date and department of hospital admission and discharge, vital status at discharge, length of stay (LOS), charge details, main and up to 6 accessory discharge diagnoses, and the most important diagnostic procedures, based on ICD-9-CM. In agreement with national dispositions by law in terms of privacy, the health authorities removed patient names, exact addresses, and other potential identifiers from the database provided for this study. University Hospital St. Anna Hospital is a teaching hospital with all facilities with more than 600 beds. The majority of admissions derive from the province of Ferrara. As previously stated, the Department of Medicine consists of 165 beds divided in four Internal Medicine units, two Infectious Disease units, and one each of Geriatrics, and Gastroenterology, patients are cared continuously, mainly admitted from ED. The great part of medical and nursing staff is permanent, covering also festive days or holidays.

3.1.2. Regional hospitalizations (Region Emilia Romagna and Region Veneto of Italy)

The Region Emilia Romagna (RER), with a surface of 22,124 Km2, is administratively divided into nine provinces (Piacenza, Parma, Reggio Emilia, Modena, Bologna, Ferrara, Ravenna, Forlì-Cesena, Rimini). The Italian National Health Service (NHS), that provides free and equal health care access to all citizens, is controlled by regional governments and administered by local health authorities. RER includes eleven local health authorities (Piacenza, Parma, Reggio Emilia, Modena, Bologna, Imola, Ferrara, Ravenna, Forlì, Cesena, Rimini), five Teaching Hospitals (Parma, Reggio

Emilia, Modena, Bologna, Ferrara) and one Research Orthopedic Institute (Bologna), with ≈ 17,000 beds for acute patients. Regional hospitalizations included all hospital admissions during an established period of time, recorded in the RER database, maintained by the Centre for Health Statistics. RER is situated in the North-East of Italy and the total population is around 4,400,000 people (~7% of Italy as a whole). Since 1999, the RER has been storing all Discharge Hospital Sheets (DHS) of patients admitted to all the regional hospitals in an electronic database. The DHS lists gender, date of birth, date and department of hospital admission and discharge, vital status at discharge, length of stay, charge details, main and up to 6 accessory discharge diagnoses, and the most important diagnostic procedures, based on the ICD-9-CM. In agreement with national dispositions by law regarding privacy, all potential identifiers were removed, and only a consecutive identification number was given to every record, corresponding to a single admission.

The archive of discharge records of Region Veneto, includes all hospitalizations of residents happening in public and private hospitals. On January 1, 2010, the total population of the Veneto Region was about 4,850,000 inhabitants, and there were about 800,000 discharges from regional hospitals each year. To comply with the national law dispositions in terms of privacy, the regional health authorities removed patient's names, exact address, and other potential identifiers from databases provided for all studies. One primary and up to 5 secondary discharge diagnoses are registered according to ICD9-CM. In Italy, hospital care is free of charge for all legal residents, who must contribute to outpatient care (laboratory tests, ambulatory care, drug costs) unless they are enrolled in lists of patients exempt from medical charges because affected by selected chronic diseases certified by a specialist.

3.1.3 National hospitalizations

The papers included all hospitalizations during an established period of time, recorded in all Italian regions. Data were obtained from the Italian National Hospital Database provided by the Ministry of Health (*Banca Dati SDO, Ministero della Salute, Direzione Generale della Programmazione Sanitaria*). The National Database includes all DHR of patients admitted to public and private hospitals in Italy. The DHR lists gender, age, date of hospital admission and discharge, department of admission and discharge, vital status at discharge (in-hospital death vs discharged alive), length of stay (in days), charge details, main and up to 5 secondary discharge diagnoses, and up to 6 procedures/interventions, based on ICD-9-CM. The Health Ministry removed patient names and other potential identifiers from the database provided for different studies in order to respect national rules on confidentiality. A consecutive identification number for each patient was the only identification data allowed in order to analyze the database for potential repeated hospital admissions of the same patient.

II. OBJECTIVES

1. GENERAL OBJECTIVE

To evaluate the importance of comorbidities recoded during hospitalization in administrative databases in order to understand management and risk factors for in-hospital mortality in the Region Emilia-Romagna of Italy.

2. SPECIFICS OBJECTIVES

- To know the relationship between comorbidity and infections in internal medicine patients.
- To evaluate risk factors for in-hospital mortality
- To test the usefulness of a comorbidity score derived from a modification of Elixhauser comorbidity index.
- To evaluate impact of hospital admissions subsequent to renal transplantation on Italian regional resources.
- To know costs and resource consuming, expressed by diagnosis related groups (DRG), related only to hospitalizations of renal transplant recipients for all causes in the Region Emilia Romagna in Italy.

III. MATERIAL AND METHODS

1. FEATURES OF THE APPROACHES MADE

Since the databases did not provide specific clinical information on each case, all analyses were limited to hard clinical indicators: fatal (death during hospitalization) and nonfatal (patient discharged alive) outcome.

We performed a descriptive analysis, and data were expressed as absolute numbers, percentages, and mean ± SD. Univariate analysis was performed to define the difference between survivors and deceased subjects; statistical analysis was performed using the Chi-square test, Student t test, and Mann–Whitney test as appropriate. Also, in order to assess the independent parameters associated with IHM, the latter was considered as a dependent variable in a logistic regression analysis, and the age, sex, and comorbidity were considered as independent ones. Odds ratios (ORs) and their 95 % confidence intervals were reported. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, 2004) was used for statistical analyses.

Moreover, aiming at evaluating the weekend effect, days of the week during which admission happended were categorized into seven 1-day intervals for analysis, and the events were classified based on their occurrence on a weekend (WE) versus a weekday (WD). Admission on WE was defined as admission during the period from midnight on Friday to midnight on Sunday. The 10 Italian festive days (January 1, January 6, April 25, May 1, June 2, August 15, November 2, December 8, December 25, and December 26), when occurring on WDs, were considered as WE. All other times were defined as WD.

2. LIMITATIONS OF OUR STUDIES EVALUATING ADMINISTRATIVE DATABASES

Firstly, the studies are observational and retrospective based on patients evaluated on ICD-9-CM code, characterized by a low sensitivity and specificity. We did not take into consideration any functional data that could be necessary for making different diagnoses. Indeed, diagnosis could be influenced from individual ability and codifying hospital procedures. Moreover, we evaluated only IHM, so our data could not consider the events in patients eventually died after transfer to other hospital or died after discharge. In addition, data based on ICD-9-CM codes could not give information on pathology severity, functional status, or intensity of care given, including aggressive therapy and devices use. Moreover, we could not ascribe any illness to any specific cause. Because of study design, we could not differentiate subjects who required invasive or non-invasive treatments from who did not. Even if we used a valid comorbidity index, it was possible that different severe diseases could had modified prognosis. Moreover, we could not evaluate the different causes of possible exacerbations, and we could not include all the available data in final analysis, so our results could be distorted. For example, in the case of renal failure, diagnosis was not based on glomerular filtration rate evaluation because we could not record biochemical parameters. On the other hand, performance of administrative data in the identification of different conditions was reported to be low, while specificity was high. Indeed, low sensibility gives reason for our result, because prevalence of the index illness could be underestimated and relationship with comorbidity could be even more important. With these limits, our studies, based on clinical evident diagnosis, considering a large population, could be considered representative of everyday clinical practices.

IV. THREE APPROACHES OF COMORBIDITY FROM INSTITUTIONAL DATABASES

1. IN-HOSPITAL MORTALITY IN INTERNAL MEDICINE ADMISSIONS COULD BE PREDICTED BY A MODIFIED ELIXHAUSER SCORE (FABBIAN F ET AL. 2017)

1.1. APPROACH STRATEGY

IHM is commonly adopted by public and private organizations and the general public as an indicator of the quality of care provided by different hospitals [Goodacre S et al 2015]. On the other hand, not all populations are comparable, multimorbidity and comorbidity should be taken into consideration at the time of IHM evaluation [Goodacre S et al 2015]. Prevalence of hospitalizations and complications after admission are higher in older adults with multiple chronic conditions [Wolff JL et al 2002]. Comorbidity is associated with worse health outcomes, as demonstrated by previous studies in the Italian health care setting [Fabbian F et al Intern Emerg Med 2016 (a), 2016 (b), 2014, 2013 (a), 2013 (b)]. However, in order to assess the impact of comorbidity or multimorbidity it is necessary to make precise measures. Evaluation of multimorbidity could be performed broadly into two ways: simple count of diseases in each individual, or scores able to assess the morbidity burden with different weights assigned to specific diseases, based on their severity and association with the risk of mortality [Valderas JM et al 2009]. The two most widely methods used in observational studies based on administrative data in order to adjust or reduce selection bias are EI and CCI [Elixhauser A et al 1998; Charlson et al 1987]. EI is built by a set of 30 conditions and CCI summarizes a weighted combination of 17 diseases. A systematic review of comorbidity indexes for administrative data showed that the EI seems to better predict mortality [Sharabiani MT et al 2012]. Moreover, van Walraven et al. [van Walraven C et al 2009] modified the EI classification system into a single numeric score for administrative data; authors found that twenty-one of the 30 conditions were independently associated with IHM. Relationship between IHM and administrative data in subjects admitted in internal medicine departments are scarce.

Our aim was to derive new weights based on internal medicine administrative data for the original EI, taking into consideration the relationship between the 30 conditions and mortality during hospitalization. The study included all hospital admissions in internal medicine department for any cause between January 1, 2000, and December 31, 2013, recorded in the hospital database. EI was calculated based on the following diseases: congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, paralysis and other neurological disorders, chronic pulmonary disease, diabetes mellitus, hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, HIV, lymphoma and cancer, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, anemia, alcohol and drug abuse, psychoses, depression (*Appendix III*). ICD-9-CM codes for EI were derived from Quan et al. [Quan H et al 2005]. We also took into consideration age, gender and diagnosis of ischemic heart disease (IHD). ICD-9-CM related to the latter diagnosis were also derived from Quan et al. [Quan H et al 2005]. IHD was included because myocardial infarction has been reported to have a high impact on health status of patients [Diederichs CP et al 2012]. All admissions were analyzed as a single record; one patient could have had different admissions through the study period since readmissions are a frequent event in internal medicine patients [Fabbian F et al 2015 (a)]. The data were expressed as absolute numbers, percentages, and means ± SD. Survivors and deceased subjects were compared for different variables by the Chi Squared, Student t or Mann Whitney U test, as appropriate. In order to evaluate the risk of IHM, logistic analysis regression was carried out determining the odds ratios with their 95% confidence interval (CI). All 30 EI conditions, age, gender and IHD were used as predictor variables. Only predictors positively associated with IHM were taken into consideration. Subsequently the method described by Sullivan et al. [Sullivan LM et al 2004] was applied in order to modify the parameter estimates of regression model into an index. The score assigned to each predictor variable was equal to its regression coefficient divided by the coefficient in the regression with the smallest absolute value, rounded to the nearest whole number. The risk of each patient was calculated by summing up the score of single predictors independently and positively associated to IHM. The risk of IHM for each possible variable was the inverse of 1 + e-(intercept+b*point total) where b is the value of the coefficient in the regression model with the smallest absolute value.

The ability of the score to discriminate between survivors and deceased was calculated using the receiver operating characteristic (ROC) curves where IHM was the outcome variable and the new score the predictor one. We compared the area under the ROC curve related to the new score and to the original EI. Finally, overall calibration was summarized using the Hosmer Lemeshow statistic [Hosmer DW et al 1997].

1.2. OBTAINED RESULTS

We analyzed 75,586 admissions between 2000 and 2013, mean age was 72.7±16.3 years, 53.4% were females and the great majority of subjects were Caucasians. IHM was 7.9% (6007 subjects) and mean score was 12.1±7.6. Hypertension, congestive heart disease, cardiac arrhythmias, chronic pulmonary disease, diabetes mellitus, liver disease, renal failure and cancer were the most frequent diseases.

Prevalence of clinical conditions defining the EI and comparison between subjects discharged alive and deceased are shown in *Table 3*. Prevalence of cardiac arrhythmias, peripheral vascular disorders, paralysis and other neurological disorders, liver disease, peptic ulcer disease excluding bleeding, and HIV was similar in the two groups, whilst prevalence of valvular disease, hypertension, chronic pulmonary disease, uncomplicated diabetes, hypothyroidism, anemia, obesity, alcohol and drug abuse and psychiatric disorders was higher in survivors than deceased subjects. All the other conditions were diagnosed more frequently in the latter group. The score was higher in deceased group (17.8±7.7 vs. 11.6±7.4, $p<0.001$).

The predictors derived from the regression model and the score derived from logistic regression analysis and transformation using the method of Sullivan et al. are reported in *Table 4*. The points assigned to each condition ranged from 0 to 16, and the possible range of the score varied between 0 and 89. In the considered population the score ranged from 0 to 54, and the risk of IHM became significant over the score of 40, overcoming the value of 60%. The relationship between the score and risk of IHM is shown in *Figure 1*.

ROC curve of the new score was 0.721 (95% CI 0.714-0.727, $p<0.001$) higher than the value obtained by the original EI index, equal to 0.656 (95% CI 0.649-0.663, $p<0.001$) (*Figure 2*).

The Hosmer-Lemeshow statistic related to the new score was statistically significant ($p<0.001$), however the association between the score and IHM could be better expressed as a non-linear relationship.

Table 3. *Prevalence of clinical conditions defining Elixhauser score and comparison between Survivors and Deceased patients.*

Variable	All patients	Survivors	Deceased	p
Number of admissions (n(%))	75,586	69,579 (92.1%)	6,007 (7.9%)	<0.001
Age (years)	72.7±16.3	72.1±16.5	79.2±12.1	<0.001
Females (n(%))	40,329 (53.4%)	37,337 (53.7%)	2,992 (49.8%)	<0.001
Ischemic heart disease (n(%))	1,946 (2.6%)	1,554 (2.2%)	392 (6.5%)	<0.001
Congestive heart failure (n(%))	12,525 (16.6%)	11055 (15.9%)	1,470 (24.5%)	<0.001
Cardiac arrhythmias (n(%))	14,619 (19.3%)	13421 (19.3%)	1,198 (19.9%)	ns
Valvular disease (n(%))	4,778 (6.3%)	4528 (6.5%)	250 (4.2%)	<0.001
Pulmonary circulation disorders (n(%))	2,424 (3.2%)	2078 (3%)	346 (5.8%)	<0.001
Peripheral vascular disorders (n(%))	4,518 (6%)	4154 (6%)	364 (6.1%)	ns
Hypertension uncomplicated (n(%))	17,958 (23.8%)	17213 (24.7%)	745 (12.4%)	<0.001
Hypertension complicated (n(%))	9,934 (13.1%)	9,338 (13.4%)	596 (9.9%)	<0.001
Paralysis (n(%))	1,536 (2%)	1,406 (2%)	130 (2.2%)	ns
Other neurological disorders (n(%))	3,298 (4.4%)	3,018 (4.3%)	280 (4.7%)	ns
Chronic pulmonary disease (n(%))	8,584 (11.4%)	7,985 (11.5%)	599 (10%)	<0.001
Diabetes uncomplicated (n(%))	12,031 (15.9%)	11,193 (16.1%)	838 (14%)	<0.001
Diabetes complicated (n(%))	1,079 (1.4%)	1,022 (1.5%)	57 (0.9%)	0.001
Hypothyroidism (n(%))	3,958 (5.2%)	3,826 (5.5%)	132 (2.2%)	<0.001
Renal failure (n(%))	7,764 (10.3%)	6,966 (10%)	798 (13.3%)	<0.001
Liver disease (n(%))	9,350 (12.4%)	8,627 (12.4%)	723 (12%)	ns
Peptic ulcer disease excluding bleeding (n(%))	390 (0.5%)	365 (0.5%)	25 (0.4%)	ns
HIV (n(%))	1,144 (1.5%)	1,039 (1.5%)	105 (1.7%)	ns
Lymphoma (n(%))	956 (1.3%)	836 (1.2%)	120 (2%)	<0.001
Metastatic cancer (n(%))	4,844 (6.4%)	3,793 (5.5%)	1,051 (17.5%)	<0.001
Solid tumor without metastasis (n(%))	9,539 (12.6%)	8,076 (11.6%)	1,463 (24.4%)	<0.001
Rheumatoid arthritis/collagen vascular diseases (n(%))	2,037 (2.7%)	1,935 (2.8%)	102 (1.7%)	<0.001
Coagulopathy (n(%))	1,196 (1.6%)	984 (1.4%)	212 (3.5%)	<0.001
Obesity (n(%))	2,835 (3.8%)	2,755 (4%)	80 (1%)	<0.001
Weight loss (n(%))	1,647 (2.2%)	1,213 (1.7%)	434 (7.2%)	<0.001
Fluid and electrolyte disorders (n(%))	3,321 (4.4%)	2,718 (3.9%)	603 (10%)	<0.001
Blood loss anemia (n(%))	766 (1%)	751 (1.1%)	15 (0.2%)	<0.001
Deficiency anemias (n(%))	2,262 (3%)	2,194 (3.2%)	68 (1.1%)	<0.001
Alcohol abuse (n(%))	1,911 (2.5%)	1,793 (2.6%)	118 (2%)	0.004
Drug abuse (n(%))	281 (0.4%)	281 (0.4%)	0 (0%)	<0.001
Psychoses (n(%))	536 (0.7%)	519 (0.7%)	17 (0.3%)	<0.001
Depression (n(%))	4,880 (6.5%)	4,816 (6.9%)	64 (1.1%)	<0.001

ns: non significant

Table 4. *Conditions independently associated with and the new score for risk of in-hospital mortality*

Variable	OR (95% C.I.)	p	Score
Age 0-60 (years)	1	-	0
Age 61-70 (years)	1.43 (1.26 - 1.62)	<0.001	3
Age 71-80 (years)	2.05 (1.84 - 2.28)	<0.001	7
Age 81-90 (years)	3.47 (3.13 - 3.85)	<0.001	11
Age 91+ (years)	5.55 (4.89 - 6.29)	<0.001	16
Renal failure	1.12 (1.03 - 1.21)	0.011	1
Male gender	1.29 (1.22 - 1.37)	<0.001	2
Other neurological disorders	1.35 (1.18 - 1.54)	<0.001	3
Lymphoma	1.60 (1.20 - 2.13)	0.001	4
Solid tumor without metastasis	1.51 (1.37 - 1.66)	<0.001	4
Ischemic heart disease	1.69 (1.39 - 2.06)	<0.001	5
Congestive heart failure	1.80 (1.66 - 1.94)	<0.001	5
Coagulopathy	2.45 (2.08 - 2.89)	<0.001	8
Fluid and electrolyte disorders	2.37 (2.14 - 2.62)	<0.001	8
Liver disease	3.01 (2.68 - 3.38)	<0.001	10
Weight loss	3.22 (2.83 - 3.67)	<0.001	11
Metastatic cancer	3.64 (3.33 - 3.98)	<0.001	12

Figure 1. *The relationship between the new score and risk of In-Hospital Mortality.*

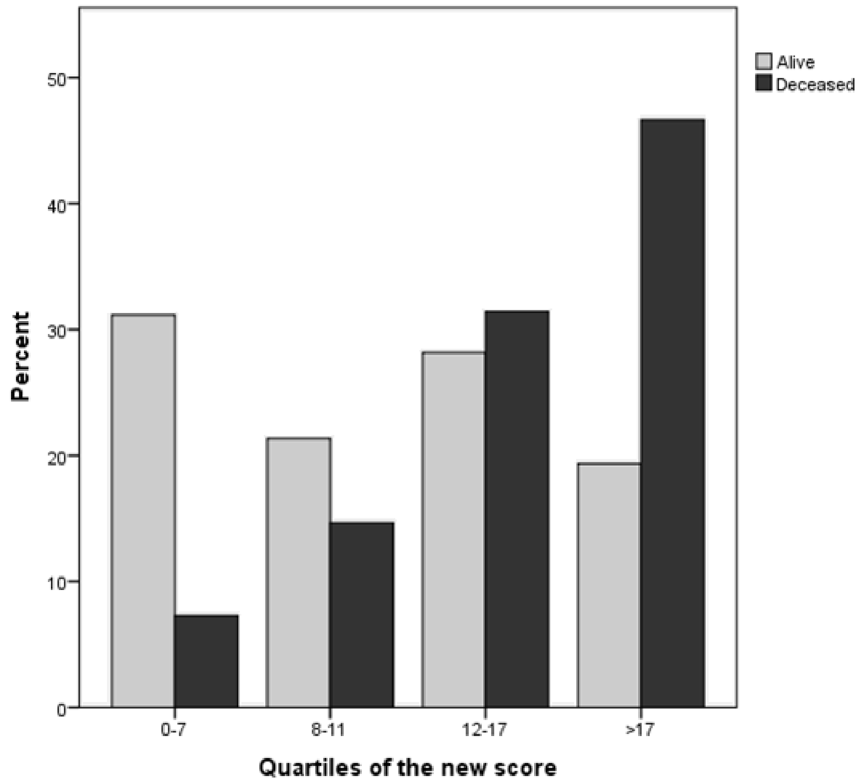
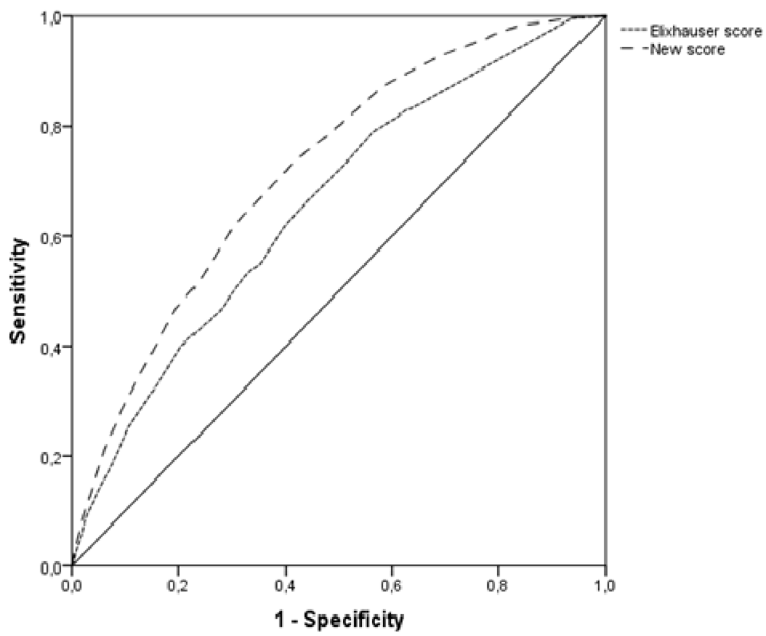


Figure 2. *Receiver operating characteristic (ROC) curve of the new score and original Elixhauser score.*



	Area under the curve	95% Confidence Intervals	p
New score	0.721	0.714-0.727	<0.001
Elixhauser index	0.656	0.649-0.663	<0.001

1.3. CONSIDERATIONS RELATED TO THE DEVELOPMENT OF THE MODIFIED ELIXHAUSER SCORE (FABBIAN F ET AL. 2017)

Multimorbidity and comorbidity are frequent in Western society; Barnett et al. analyzed cross-sectionally 1,751,841 people registered with 314 medical practices in Scotland, 42.2% of all patients had one or more morbidities and 23.2% were multimorbid, especially older adults [Barnett K et al 2012]. An enormous effort is required by health care professionals in order to manage such a large number of patients. An inadequate care could be the consequence of a mistake in prognosis prediction, ending up in waste of resources. In internal medicine, prognostic indexes could suggest a better clinical decision-making process, especially in older adults with multimorbidity. In elderly hospitalized population both social and clinical data have been used to predict mortality [Walter LC et al 2001; Cei M et al 2015; de Gelder J et al 2016]. Escobar et al. [Escobar GJ et al 2008] developed a model including sex, age, admission type, a laboratory-based acute physiology score and a comorbidity score based on administrative data to predict IHM and 30-day mortality evaluating more than 250,000 patients. Recently in Europe two scores have been evaluated, the National Early Warning Score (NEWS) [Abbott TE et al 2016] and the PROFUND index [Bernabeu-Wittel M et al 2016], both based on clinical data. In Italy data regarding a score summarizing patients' clinical condition and IHM are scarce. Prediction of the risk of IHM represents a key factor in the management of elderly hospitalized patients, however mortality in older adults results from a combination of biological, functional, nutritional, psychological and environmental factors, not easily collected during admission. Di Bari et al. evaluated prognostic stratification of older patients with complex medical problems among those who accessed the emergency department (ED). They examined the discharge records of more than 10,000 older adults admitted during 2005 to the ED in Florence, Italy. Using information on demographics, drug treatment, previous hospital admissions, and discharge diagnoses, they developed a 1-year mortality prognostic index. The higher the index, the higher the mortality, however patients with worse prognostic index scores appeared to benefit from admission in a geriatrics compared with an internal medicine ward [Di Bari M et al 2010]. Mazzaglia et al. [Mazzaglia G et al 2007] developed and validated a mortality and hospitalization prognostic score based upon information readily available to primary care physicians (PCPs). Prognostic indexes were developed in 2,470 and validated in 2,926 older subjects living in Florence, Italy, evaluating fifteen-month mortality and hospitalization. They considered the following predictors: patient demographics, a seven-item questionnaire on functional status and general health, use of five or more drugs, and previous hospitalization. They concluded that predictors of death and hospitalization in older community-dwelling people can be obtained with two indexes using information easily available to PCPs. A Multidimensional Prognostic Index (MPI) predicting short- and long-term mortality derived from a standardized Comprehensive Geriatric Assessment (CGA) was studied. Pilotto et al. [Pilotto A et al 2008] suggested that MPI was associated with 1-year mortality investigating 838 and 857 elderly hospitalized patients as development and validation groups respectively. The CGA included clinical, cognitive, functional, nutritional, and social parameters and was carried out using six standardized scales and information on medications and social support network. MPI was developed from CGA data by aggregating the total scores. In both cohorts, higher MPI scores were significantly associated with older age, female gender, lower educational level, and higher mortality. Authors calculated the area areas under the ROC curves and it was 0.75 [Pilotto A et al 2008]. Sancarlo et al. [Sancarlo D et al 2011] compared prediction of mortality of the MPI modifying the nutritional assessment. They conducted a prospective study with a one-year follow-up including more than 4,000 hospitalized patients aged 65 years and older. A standardized CGA that included information on functional, cognitive, risk of pressure sore, comorbidities expressed as Cumulative Illness Rating Scale (CIRS), medications, living status and nutritional status was used to calculate the MPI using a previously validated algorithm. Higher MPI values were significantly associated with higher mortality rates both after 1-month and 1-year of follow-up. Rozzini et al. [Rozzini R et al 2001] applied the score developed by Walter et al. [Walter LC et al 2001] performing a multidimensional evaluation, recording age, gender, education, living style and conditions, availability of support, cognitive and affective status, physical health and functional abilities. They enrolled 940 subjects aged 75 years and more hospitalized in an elderly medical unit. Authors evaluated 6 months' mortality and male sex, dependency in 1-4 activities of daily living (ADL) at discharge, dependency in all 5 ADL, congestive heart failure, solitary and metastatic cancer, serum creatinine levels higher than 3 mg/dl, low albumin were all predictive factors. The same score was also evaluated in predicting IHM by Cei et al. [Cei M et al 2015]. Authors retrospectively revised the medical records of 1,004 patients admitted between April and December 2013. Data regarding gender, activities of daily living, comorbidities, and routine laboratory tests were used to calculate a modified Walter score. The latter showed a good prognostic accuracy (ROC = 0.81; 95%CI 0.78- 0.84). All the above-mentioned scores developed by Italian researchers are not promptly available at the time of patients' admission, because they need time to be calculated. On the contrary a score based on diseases possibly already recorded in patients' files could suggest an immediate risk for IHM that physicians could evaluate also during night-time shifts and weekends.

To the best of our knowledge our modified EI is the first one that has been developed using administrative data in Italy, and that could be calculated automatically. Thompson et al. recently derived weighted summary scores to predict IHM replicating van Walraven index [van Walraven C et al 2009] using the full (30 items) and reduced (29 items) set of comorbidities. They evaluated the 2009 Maryland State Inpatient Database enrolling 228,565 inpatient admissions to 50 community hospitals. Mean age of patients was 59.9±18.7 years and IHM was 2.2%. They concluded that the scores were statistically superior to summaries using simple comorbidity counts in predicting IHM [Thompson NR et al 2015]. Our design is similar to the van Walraven's one [van Walraven C et al 2009]. The main difference consists on the fact that we excluded from the final score all conditions that were not positively associated with IHM when logistic regression analysis was performed.
Score systems have been developed in order to enhance the accuracy of prognosis, in fact physicians are often asked to make prognostic assessments being conscious that their assessments could be inaccurate. Evaluation of prognostic systems is based on calibration and discrimination, i.e. accuracy and reproducibility and transportability, i.e. generalizability. The ability to produce accurate predictions among patients not included in the development of the system but from the same population defines reproducibility, whilst the ability to produce accurate predictions among patients drawn from a different but plausibly related population defines transportability. It should be also considered that considering a single historical period, geographic location, methodological approach, or follow-up interval could limit the generalizability of a prognostic system [Justice AC et al 1999]. Hasia et al. suggested that ICD-9-CM coding is not reliable [Hsia DC et al 1988]. On the other hand, recently Mazzali & Duca [Mazzali C & Duca P 2015] carefully analyzed advantages and disadvantages in the use of administrative data. Population coverage, very large sample size, heterogeneity of covered population, long observation periods, up to date information, low costs and possibility to link several different sources of information were mentioned as advantages, while absence of a previous research plan, lack of specific clinical information, effect of administrative use (i.e. reimbursement), possible misclassification of outcomes, difficulties to control confounding factors were mentioned as disadvantages.
A different frequent limitation of administrative data is the lack of present-on-admission information, making difficult to distinguish acute conditions developing during hospital stay (i.e. complications of care). On the other hand, in the development of modified EI we did not consider the single cause of admission, but all ICD-9-CM codes indicating the whole patients' history.
Modified EI does not take into consideration the reason for and urgency of admission, parameters that could have an impact on outcome. Moreover, we considered hospitalizations and a single patient could have different admissions with different scores depending on the ICD-9-CM coding.

Score calculation could vary between hospitals depending on clinical coders performance or financial incentives such as diagnosis-related groups or healthcare-related groups. However, our outcome could be considered a hard one being IHM. Obviously, we had no information about out-of-hospital mortality.

It has been underlined that there is heterogeneity of existing multimorbidity indexes, most frequently reported conditions being diabetes mellitus, stroke, hypertension and cancer [Diederichs C et al 2011]. Our index could increase such heterogeneity, on the other hand we considered diseases commonly encountered in internal medicine patients and we focused on IHM, therefore only conditions related to it were considered.

Finally, the term prognostic index is not included in the Medical Subject Heading databases in PubMed, making it difficult to exactly identify studies dealing with IHM.

Baseline multimorbidity or comorbidity adjustment is a crucial point in clinical practice and research. In order to make prognostic assessment, physicians could include diseases individually or through the use of summary measures. Multiple chronic diseases and the related prescription of multiple medications are everyday clinical practice in internal medicine departments [Mannucci PM & Nobili A 2014], therefore a prognostic score could help physicians in targeting interventions in older adults, identifying subjects at high risk for IHM. However, at the moment, there is not sufficient evidence to recommend widespread use of modified EI in clinical practice. The next step should be to prospectively validate our index (APPENDIX IV) in different populations.

2. INFECTIONS AND INTERNAL MEDICINE PATIENTS: COULD A COMORBIDITY SCORE PREDICT IN-HOSPITAL MORTALITY? (FABBIAN F ET AL. 2018)

2.1. CURRENT STATUS OF THE ISSUE

Increasing population life expectancy and mean age of population are the fundamental basis of growing morbidity, hospital admissions and mortality in older patients [Green JE et al 2014]. World Health Organization reports show that infectious diseases are responsible for an age specific death rate of 76.3x100.000 population globally, and 11.4 in Italy [Available at: www.who.int/healthinfo/global_burden_disease/estmates/en/index1.html (accessed 05/08/2019)]. De Buyser et al. evaluated 1223 patients aged more than 81 years admitted in geriatric and internal medicine acute wards of seven Italian hospitals, and infections represented 11% of medical diagnoses, being also independent predictors of hospital LOS [De Buyser SL et al 2014]. Our group has previously reported that IHM was independently associated with sepsis, urinary tract infections, female gender, and age [Fabbian F et al 2015 (b)]. Moreover, IHM has been found to be independently associated with several comorbidities, such as renal dysfunction, myocardial infarction, stroke, and severe chronic obstructive pulmonary disease [Fabbian F et al 2013 (b); Fabbian F el at 2014; Fabbian F et al 2016 (a)]. A European study by Esteban et al. [Esteban A et al 2007] evaluated 15,852 patients aged >18 years admitted to hospitals. The calculated incidence of sepsis was 367 cases per 100,000 adult area residents per year, and the cumulative incidence rate among patients admitted to the hospital was 4.4%. In 71% of cases the infection was community-acquired, and severe sepsis and septic shock showed an incidence rate of 104 and 31 cases per 100,000 adult area residents per year, respectively. Only 32% of severe sepsis patients received intensive care, and IHM was 12.8%, higher for severe sepsis (20.7%) and septic shock (45.7%) [Esteban A et al 2007]. Unfortunately, data about IHM due to infectious disease in internal medicine wards (IMW) are scarce. Infections represent severe clinical conditions, that could rapidly worsen and end up in IHM.

The aim of this study was to evaluate the risk factors for IHM in a large series of patients consecutively admitted to IMW for infectious diseases by using ICD-9-CM codes, and to test the possible usefulness of a comorbidity index, proposed by the authors and adapted for internal medicine patients, as a predictor of IHM.

2.2. METHODS

2.2.1. Patients selection and eligibility

This retrospective study, conducted in agreement with the declaration of Helsinki, and approved by the local ethical committee, included all hospital admissions in internal medicine department due to infectious diseases between January 1, 2013, and December 31, 2016 recorded in the database of the General Hospital of Ferrara.

2.2.2. Data Collection

All patient admitted to the Department of Medicine units with an infectious diseases diagnosis in any position were included in our study (ICD-9-CM codes: 001-139, 421, 422, 460- 466, 480- 487, 567, 575.0–575.1, 577.0, 590-599, 680-686, 711, 730). Subjects transferred to surgical departments or intensive care units (ICUs) were excluded, due to the fact that management is completely different and admission in these type of wards is decided by specialists. Readmissions are commonly seen amongst medical patients [Fabbian F et al 2015 (a); De Giorgi A et al 2016], therefore we selected to amalgamate multiple admissions for single patients as single record. Diagnosis of sepsis and different infections such as pulmonary, gastrointestinal, cutaneous infections, endocarditis, and other site of infections were classified by ICD-9-CM codes. ICD-9-CM codes were also needed to calculate a modified EI, a novel score recently proposed by our group in order to take into due account the comorbidity burden [Fabbian F et al 2017] (Appendix IV). The following conditions were considered for score calculation: age, gender, presence of neurological disorders, lymphoma, solid tumor with metastasis, ischemic heart disease, congestive heart disease, coagulopathy, fluid and electrolyte disorders, liver disease, weight loss, and metastatic cancer [Fabbian F et al. 2017]. The score was developed using administrative data and was calculated automatically. Points assigned to different conditions in order to calculate the score for risk of IHM are reported in *Table 5*. Finally, IHM related to these patients was extracted from the general database.

2.2.3. Statistical analysis

The data have been expressed as absolute numbers, percentages, and means ± SD. We compared survivors and deceased during admission, and the analysis of the variables was conducted using Chi

Squared, Student t-tests or Mann Whitney U test, as appropriate. Moreover, in order to assess the independent parameters associated with IHM, the latter was considered as a dependent variable in a logistic regression analysis, and different infections classified as reported above and comorbidity score were considered as independent ones. Odds ratios (ORs), and their 95% confidence intervals (95% CI) were reported.

The ability of the score to discriminate between survivors and deceased was calculated using the Receiver Operating Characteristic (ROC) curves, in which the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points [Hanley JA 2014]. For the construction of this curve, IHM was the outcome variable and the novel score was the predictor variable. Accuracy is measured by the area under the curve (AUC). All p-value were two tailed, and a p-value <0.05 was considered significant. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, 2004) was used for statistical analyzes.

2.3. OBTAINED RESULTS

During the study period, we analyzed 12,173 records corresponding to 253.6 admissions due to infectious diseases per month. Mean age was 64.8 ± 25.1 years, females were 66.2%, 9.3% developed sepsis and 12.7% of cases died. Clinical characteristics of our population is reported in *Table 6*. Mean value of comorbidity score was 12.3 ± 9.7, and it was significantly higher in deceased patients (18.1±9.1 vs 11.4±9.5, p<0.001). Difference between survivors and deceased patients are reported in *Table 7*. Due to the fact that in a patient more than one infection could be diagnosed the number of infections was higher than the number of admission.

At multivariate analysis, in decreasing order, sepsis (OR 5.961; 95%CI 5.187–6.850, p<0.001), endocarditis (OR 4.247; 95% CI 2.492-7.238, p<0.001), pulmonary infections (OR 1.905; 95% CI 1.455-2.494, p<0.001), other sites of infection (OR 1.671; 95% CI 1.242-2.249, p=0.001), and urinary tracts infections (UTIs) (OR 0.548; 95% CI 0.419-0.715, p<0.001), were independently associated with IHM (*Table 8*). The modified EI (OR 1.070 per unit of increasing score), resulted to be independently associated with IHM as well. Thus, a weighted extrapolation obtained by multiplying 1.070 for the mean value of the score in the deceased patients, produced a weighted score of 19.367, (95% CI 19.258-19.475), much higher even than the risk due to development of sepsis (*Table 8, Figure 3*). Receiver Operating Characteristic (ROC) analysis (*Figure 4*) showed that comorbidity score and development of sepsis were significant predictors for IHM (Area Under the Curve, AUC: 0.724 and 0.670, respectively).

Table 5. *Points assigned to different conditions in order to calculate the score for risk of in-hospital mortality (Fabbian F et al. 2017)*

Variable	**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
Renal failure	1
Male gender	2
Other 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
Weight loss	11
Metastatic cancer	12

Table 6. *Clinical characteristics of 12,173 records related to patients admitted to internal medicine wards due to infectious diseases.*

Characteristics	Data
Total	12,173
Male (n(%))	4,120 (33.8)
Female (n(%))	8,053 (66.2)
Age (years)	64.8±25.1
Pulmonary infections (n(%))	4,172 (34.3)
Urinary tract infections (n(%))	2,135 (17.5)
Gastrointestinal infections (n(%))	2,071 (17)
Cutaneous infections (n(%))	269 (2.2)
Endocarditis (n(%))	103 (0.8)
Other infections sites (n(%))	4,111 (33.8)
Sepsis (n(%))	1,138 (9.3)
Comorbidity score	12.3±9.7
Deceased (n(%))	1,545 (12.7)

Table 7. *Comparison between survivors and deceased patients.*

Variable	Survivors (n=10,628)	Deceased (n=1,545)	p
Male (n(%))	3,593 (33.8)	527 (34.1)	NS
Female (n(%))	7,035 (66.2)	1,018 (65.9)	
Age (years)	62.8±25.8	78.6±13.6	<0.001
Pulmonary infections (n(%))	3,503 (33)	669 (43.3)	<0.001
Urinary tract infections (n(%))	1,945 (18.3%)	190 (12.3%)	<0.001
Gastrointestinal infections (n(%))	1,926 (18.1%)	145 (9.4%)	<0.001
Cutaneous infections (n(%))	250 (2.4%)	19 (1.2%)	0.005
Endocarditis (n(%)	79 (0.7)	24 (1.6)	0.001
Other infections (n(%))	3,514 (33.1%)	597 (38.6%)	<0.001
Sepsis (n(%))	639 (6%)	499 (32.3%)	<0.001
Score	11.4±9.5	18.1±9.1	<0.001

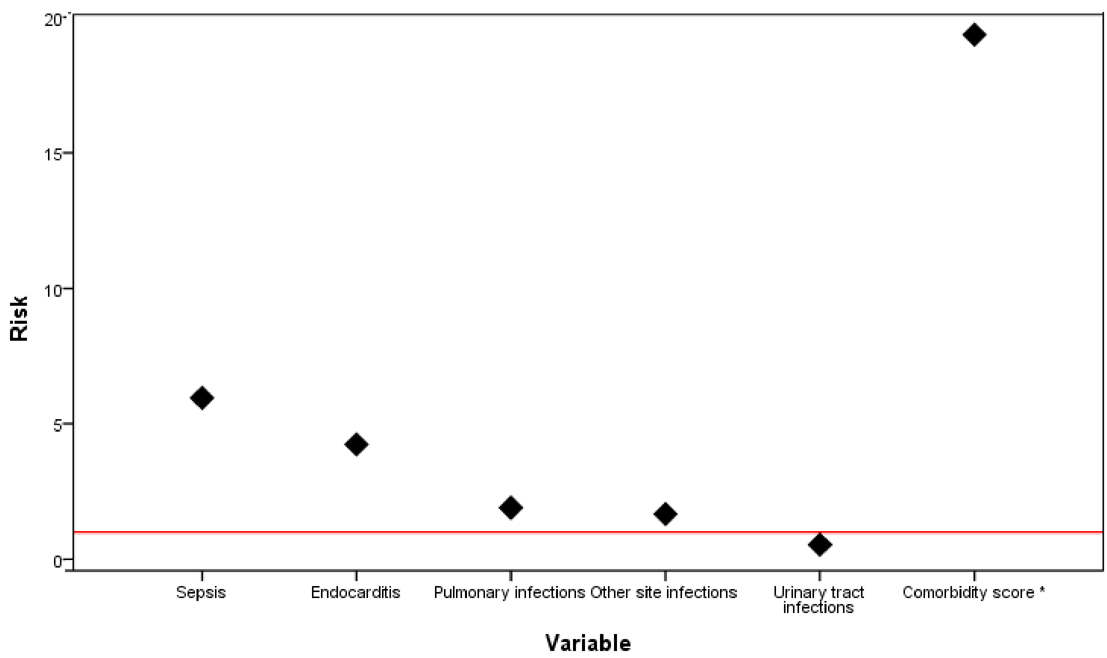
NS: Non significative

Table 8 *Multivariate analysis results showing variable independently associated with in-hospital mortality.*

Variable	**OR**	**95% CI**	**p**
Development of sepsis	5.961	5.187–6.850	<0.001
Endocarditis	4.247	2.492-7.238	<0.001
Pulmonary Infections	1.905	1.455-2.494	<0.001
Other sites infections	1.671	1.242-2.249	0.001
Urinary tract infections	0.548	0.419-0.715	<0.001
Comorbidity score (per unit of increasing score)	1.070	1.064-1.076	<0.001
Weighted comorbidity score*	19.367	19.258-19.475	NC

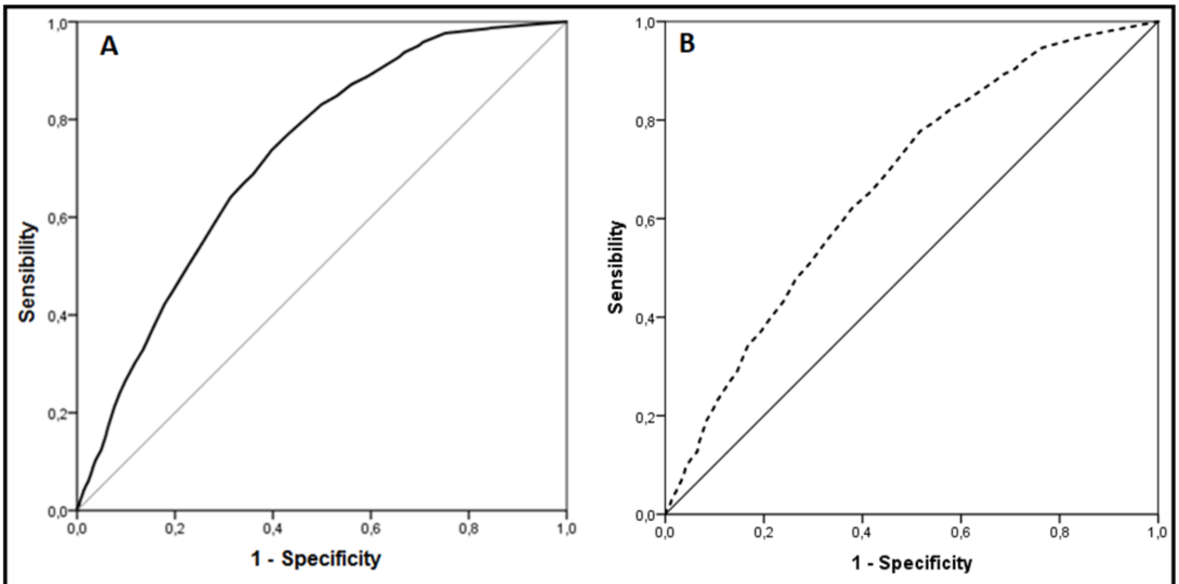
*Weighted comorbidity score was calculated as the risk due to every unit of comorbidity score was multiplied for the mean value of the score in the deceased patients. CI: Confidence Intervals; NC: Not Calculated

Figure 3. *Multivariate analysis results relating association between in-hospital mortality and development of sepsis, comorbidity and different infectious diseases.*



*Weighted comorbidity score was calculated as the risk due to every unit of comorbidity score was multiplied for the mean value of the score in the deceased patients.

Figure 4. *Receiver Operating Characteristic (ROC) curves analysis showing the relationship between in-hospital mortality and comorbitidy score (A) and development of sepsis (B).*



AUC	95% C.I.	p
0.724	0.712 - 0.736	<0.001

AUC	95% C.I.	p
0.670	0.655 - 0.685	<0.001

2.4. LIMITATIONS AND STRENGTHS

We are aware of several limitations of our study. First, this is a cross observational retrospective study based on ICD-9-CM codes, characterized by a low sensitivity and specificity [Hsia DC et al 1988]. Data based on ICD-9-CM codes are characterized by low sensitivity and specificity, and do not provide information on reason for admission, specific cause of death, disease severity, microbial blood isolation, functional status, intensity care level, including aggressive therapy and/or devices use. We are aware that description of the micro-orgasm that caused the infection would be interesting, especially in differentiating community and health related infections, however due to our study design this information is lacking.

Recently it has been developed a clinical model for predicting IHM in unselected acute medical admissions including age, body mass index, mean arterial pressure on admission, prior admission within 3 months, heart failure, active malignancy, and chronic use of statins and antiplatelet agents [Sakhnini A et al 2017]. Moreover, mortality risk of pediatric sepsis patients was assessed extracting data of admission to the pediatric ICU. Authors identified 6 variables associated with IHM such as brain natriuretic peptide, albumin, total bilirubin, d-dimer, lactate levels and mechanical ventilation [Chen M et al 2017]. Many of the above-mentioned parameters were not evaluated in our study, they were available in the analyzed database based on ICD-9-CM.

Lack of specific clinical information, effect of administrative use (i.e. reimbursement), possible misclassification of outcomes, and difficulties in controlling confounding factors can be considered evident disadvantages [Mazzali C & Duca P 2015]. Second, this is a single center study, with the great majority of Caucasian ethnicity only, and results could be different if several hospitals or different ethnic groups would be included. Generalization of a prognostic model can be limited by a given historical period, geographic location, methodological approach, or follow-up interval [Justice AC et al 1999]. Moreover, the model tested in the present study should be prospectively validated. Third, we had no information about out-of-hospital mortality.

However, some possible strengths may also be considered. To the best of our knowledge, this is the first study conducted in IMW in Italy. The population size is not negligible, and IHM represents a hard outcome. Again, analysis of administrative data has also some pros: it allows analysis to wide population coverage and large sample size, long observation periods, low costs, and possibility to link several different sources of information. Moreover, there is also convincing evidence that use of administrative data makes possible to predict hospital admissions and complications [Wallace E 2014].

Careful evaluation of comorbidity in internal medicine patients is nowadays matter of extreme importance [Kusumastuti S et al 2017; Romero-Ortuno R et al 2016; Rossi PD et al 2016; Marengoni A et al 2016]. This seems to be true also in the case of patients hospitalized to IMW for infectious diseases. In fact, the results of this study, show that IHM depends, in addition to type and site of infection, also on concomitant comorbidities. Thus, in this kind of patients, especially elderly, a careful evaluation of comorbidity status by means of a simple score could represent a fundamental step in the disease management.

2.5. CONSIDERATIONS ON THE PREDICTIVE CHARACTER OF COMORBIDITY SCORE

To the best of our knowledge, this is the first Italian study conducted in IMW evaluating impact of comorbidity on IHM due to infections. As previously stated, our group has proposed and evaluated a modified version of the EI on IHM due to all causes [Fabbian F et al 2017]. We performed a single-center retrospective study including hospital admissions for any cause in the department of internal medicine, and compared the EI with a new score obtained from EI. Prediction power of the new index was higher than the original EI. The new score included age, gender, presence of neurological disorders, lymphoma, solid tumor with metastasis, ischemic heart disease, congestive heart disease, coagulopathy, fluid and electrolyte disorders, liver disease, weight loss, and metastatic cancer [Fabbian F et al 2017]. With this study, we decided to test the ability of a simple comorbidity score, based on administrative data, to predict IHM in subjects admitted for infections. On one hand, development of sepsis represents the strongest risk factor for IHM in this kind of subjects. This is not surprising at all, since sepsis is a prevalent and severe medical condition and its incidence is increasing [Gaieski DF et al 2013]. On the other, comorbidity score has resulted to be a significant predictor of IHM as well. In fact, since comorbidity score gives additional OR of 1.070 per unit, the final calculated adapted risk, is even higher than that of sepsis.
Physicians should take into consideration patients with their burden of illness in their clinical practice and comorbidity appears to be crucial also in research. In order to improve prognostic assessment, patients could be assessed by every individual disease or through a number suggesting the burden of illness. Such a number could be related to multiple chronic diseases and prescription of multiple drugs, helping physicians in targeting intervention, and identifying subjects that could be at risk of serious adverse events. We think that the use of clinical scores could really help physicians in clinical practice. Relationship between mortality, comorbidity and infectious diseases has been considered by different authors, results are not univocal, probably due to different study

design, patients' selection and settings. In their retrospective study, Briongos-Figuero et al. [Briongos-Figuero LS et al 2015] compared 187 deaths due to infectious causes and 224 deaths due to non-infectious causes (mean age >80 years for both groups). Comorbidity was evaluated by CCI. Dementia, cerebrovascular disease, living in nursing home and being dependent were risk factors for IHM due to infectious disease. CCI was not different in the two groups of patients, but in this study the authors took into consideration only fatal cases [Briongos-Figuero LS et al 2015]. Yang et al. [Yang Y et al 2010] assessed the disease burden of sepsis and evaluated the impact of CCI and age as risk-adjusted hospital mortality predictors in patients with sepsis using hospital administrative database. They studied more than 300,000 hospitalized patients over four years, of whom 6,929 (2.27%) had sepsis, and 1,216 were admitted to ICU. The mortality rates increased consistently in patients with CI ranging from none to low, moderate and high grade for both patients with ICU admission (39.4%, 51.6%, 55.9%, and 54.3% respectively) and patients without ICU admission (6.4%, 8.7%, 17.1%, and 25.3% respectively). Logistic regression analysis showed that CCI (OR 11.8) and age (OR 8.46) were independently associated with IHM [Yang Y et al 2010]. Since the comorbidity score used in our study just included age, we did not include this variable in the model to avoid overestimation bias. Mazzone et al. [Mazzone A et al 2016] evaluated short-term mortality in 533 septic patients treated in IMW, of whom 78 (14.6%) died during hospitalization. Cardio-cerebrovascular disease, diabetes, chronic kidney disease, respiratory disease, active cancer or hepatic disease were the comorbid conditions considered by authors. Mortality rate was 5.5% in subjects with non-severe sepsis and 20.1% in those with severe sepsis or septic shock. Severe sepsis or septic shock (OR 4.41), active solid cancer (OR 2.14), immune system weakening (OR 2.10), and age (OR 1.03 per year) were independently related to mortality [Mazzone A et al 2016]. Rebelo et al. [Rebelo M et al 2011] assessed independent risk factors for IHM studying retrospectively a cohort of 135 patients with bacteremia aged ≥65 years, admitted to an IMW. IHM was 22.2% and in more than 45% of subjects the cause was urinary tract infections. The main microorganisms isolated in the blood cultures were Escherichia coli (14.9%), Methicillin-resistant Staphylococcus aureus (MRSA) (12.0%), non-MRSA (11.4%), Klebsiella pneumoniae (9.1%), and Enterococcus faecalis (8.0%). IHM was independently associated, in decreasing order, with bacteremia of unknown focus (OR 8.673), chronic renal disease (OR 6.179), cognitive impairment at admission (OR 3.621), and age ≥ 85 years (OR 2.812), whereas different chronic medical conditions were equally distributed in survivors and deceased patients [Rebelo M et al 2011].

It has to be stressed that sometimes studies are not easily comparable due to the application of scores utilized, for example, in the EDs or ICUs, often requiring data unavailable in IMW. In fact, in the ED settings different clinical scores were tested in order to identify the high risk infected patients, but such scores showed heterogeneous ability to predict hard outcomes such as 28-day mortality or IHM, due to different clinical manifestations related to sites of infection, comorbidity, and underlying microorganisms. The MEDS (Mortality in Emergency Department Sepsis) score [Shapiro NI et al 2003] was one of the first clinical scores for emergency settings used to predict the 28-day mortality risk, and its AUC was 0.82. A few years later, Sankoff et al. [Sankoff J et al 2006] tried to propose a modified MEDS score (mMEDS), removing the lack of neutrophil band counting, but final predictivity was the same (AUC: 0.82). Ghanem-Zoubi et al. [Ghanem-Zoubi NO et al 2011] evaluated the ability of either MEDS and another 3 scoring systems: modified early warning score (MEWS), simple clinical score (SCS), and rapid emergency medicine score (REMS). In order to stratify for utilization management, performance assessment, and clinical research, they studied 28-day and overall IHM, and 30- and 60-day mortality in 1,072 patients meeting sepsis criteria and admitted to IMW. The AUC for each scoring system was 0.73-0.75 for MEDS, 0.65-0.70 for MEWS, 0.76-0.79 for SCS, and 0.74-0.79 for REMS [Ghanem-Zoubi NO et al 2011]. All these scores, however, were characterized by collection of different clinical information, such as heart rate, temperature, systolic blood pressure, but information on comorbidity was scarce.

Again, different score systems for severity of illness have been validated as tools to predict the risk of death in ICU patients, but a systematic review performed by Calle et al. [Calle P et al 2012] did not provide enough information to assess the accuracy of the prognostic models in patients with suspected infection admitted to the ED and hospital ward. More recently, Chen et al. [Chen YX & Li CS 2014] compared the prognostic performance of MEDS and other two clinical scores, the Predisposition, Infection, Response and Organ dysfunction (PIRO) staging system, and the Acute Physiology and Chronic Health Evaluation (APACHE II) scores in patients admitted to ICU. All 3 systems were independent predictors of 28-day mortality with similar AUC values. The AUC of PIRO was 0.889 for ICU admission, 0.817 for multiple organ dysfunction [Chen YX & Li CS 2014].

In this study, we found that UTIs had protective effect for IHM. In a previous investigation [Fabbian F et al 2015 (b)] we analyzed retrospectively diagnosis of UTIs based on ICD-9-CM codes and IHM, five percent of cases developed sepsis and 3.7% had a fatal outcome. The latter percentage was less than one third of the mortality recorded in this study, moreover development of sepsis was independently related to IHM. It could be that physicians early recognize UTIs, especially in subjects with high comorbidity, suggesting the beginning of specific treatment.

3. IMPACT OF HOSPITAL ADMISSIONS SUBSEQUENT TO RENAL TRANSPLANTATION ON ITALIAN REGIONAL RESOURCES: A RETROSPECTIVE STUDY IN THE REGION EMILIA-ROMAGNA OF ITALY (FABBIAN F ET AL. 2019)

3.1. CURRENT STATUS OF THE ISSUE

Treatment of end-stage renal disease (ESRD) consumes an important amount of resource of health service. Patients with chronic kidney diseases (CKD) often present many comorbidities [Rao A et al 2013] requiring hospitalizations during acute phases, and therefore additional costs [Metcalfe W et al 2003]. A 50% increase in the serum creatinine value was related to an excess of hospital costs of ~$ 5,510 [Chertow GM et al 2005]. It has been reported that CKD worsened in-hospital outcome of patients after admission for myocardial infarction [Fabbian F et al 2013 (b)], ischemic/hemorrhagic stroke [Fabbian F et al 2014] and chronic obstructive pulmonary disease [Fabbian F et al 2016 (a)]. Smith et al. evaluated more than 13,000 patients with CKD and depending on stage, cases had 1.9 to 2.5 times more prescriptions, 1.3 to 1.9 times more outpatient visits, were 1.6 to 2.2 times more likely to have had an inpatient stay, and had 1.8 to 3.1 more stays than controls. The mean amount of money that was needed for each patient during the 66 months' follow-up was $38,764 in stage 2, $33,144 in stage 3, and $41,928 in stage 4 [Smith DH et al 2004]. Similar results were found in Germany by Baumeister et al [Baumeister SE et al 2010] in 2010. It was also calculated that annual Medicare expenses attributable to CKD were $1,700 for stage 2, $3,500 for stage 3, and $12,700 for stage 4, per each patient. Costs increased as disease severity worsened [Honeycutt AA et al 2013]. In Italy, it has been estimated that the unadjusted estimated mean annual social costs of a patient with stage 4 and stage 5 CKD were € 9,514 and 11,152, respectively [Turchetti G et al 2017]. An Italian study from Lombardy Regional Health Service reported that direct healthcare cost/patient were € 5,239, € 12,303 and € 38,821 during the 24-12 months' pre-dialysis, 12-0 months' pre-dialysis and in the first year of dialysis periods, respectively [Roggeri A et al 2017]. A recent study from Korea reported that medical cost per year per renal transplant patient was € 68,798 [Kim SH et al 2017].

Renal transplantation has been established to represent the gold standard of renal replacement therapy, providing better outcomes in terms of survival, quality of life and cost effectiveness ratio, compared to other replacement methods [Wolfe RA et al 1999; McDonald SP & Russ GR 2002; Cavallo MC et al 2014], however costs due to frequent hospitalization in RTRs are still a matter of debate. It has been shown that peripheral vascular diseases and diabetes were associated with significantly higher costs in RTRs [Li B 2017], and that hospitalization accounted for 27% of the costs [Couillerot-Peyrondet A-L, 2017]. A method for assessing the economic impact of hospitalizations in all categories of patients is evaluation of diagnosis related groups (DRG) codes of hospital discharge. In fact, analysis of DRG codes is a worldwide well recognized method able to relate hospital activities to health care expenses.

The aim of this study was to investigate costs and resource consuming related to hospitalizations, analyzing DRG due to hospital admissions of RTRs after the kidney transplantation operation in the region Emilia Romagna (RER) in Italy.

3.2. METHODS

This retrospective study, conducted in agreement with the declaration of Helsinki of 1975, revised in 2013, included all hospital admissions of RTRs which happened between January 1, 2001, and December 31, 2015, recorded in the database of the RER of Italy, and maintained by the Center for Health Statistics (Management Planning and Control Service). RER belongs to North-East of Italy and total population is around 4,400,000 people (~7% of the entire country).

The study included only RTRs, considering all cases of admission with any complications recorded from 2001 to 2015. The inclusion criterion was the identification of the ICD-9-CM code V420. Every admission was associated to DRG in order to pay hospital activity. DRG have been considered the best way to evaluate hospitals' efficiency by most stakeholders. We calculated number of admissions, number of RTRs, inhabitants of the RER, rate of admissions, rate of admitted RTRs, mean age, LOS as total number of days, mean and median days, mean value of DRG and costs of admissions during the 15-year period of the study.

All admissions of different RTRs were analyzed as a single record, so that one patient could have had different admissions, therefore readmissions were not considered being a frequent event in this population. Data are expressed as absolute numbers, means, and median in each year follow-up duration.

Statistical analysis was performed using SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, 2004, for statistical analysis of the demographic data.

3.3. OBTAINED RESULTS

During the 15-year period of the study we evaluated 14,558 admissions of whom 14,186 were discharged from acute wards and 372 from post-acute ones. Mean age of admitted patients was 56.6±1.6 years. Discharges took place from nephrology units in 21.2%, renal transplant units in 19.3%, internal medicine units in 13.2%, general surgery units in 10.8%, cardiology units in 7.9%, gastroenterology units in 3.3%, pediatrics units in 2.5% and other different units in 21.4% of cases. Number of admissions increased from 724 in 2001 to 1,099 in 2015 (*Figure 5*). In the same way mean age of admitted patients increased from 48.1 to 54.4 years during the study period (mean age was 48.1 years in 2001, 49.9 in 2002, 52.2 in 2003, 51.9 in 2004, 50.6 in 2005, 52.7 in 2006, 53.1 in 2007, 53 in 2008, 53.4 in 2009, 53.3 in 2010, 52.4 in 2011, 54.2 in 2012, 55.6 in 2013, 55.6 in 2014, and 54.4 in 2015).

Number of admissions, number of admitted RTRs, inhabitants of the region Emilia-Romagna (RER) of Italy, rate of admissions, rate of admitted RTRs, LOS, mean value of DRG and costs of admissions during the 15-year period of the study are reported in *Table 9*. The total number of RTRs admitted in the study period was 9,197 and mean rate of admitted RTRs (*100,000) was 14.21. Mean rate of admission (*100,000) in the 15 year was 22.50. Total, mean and median LOS were 122,966, 8.7 and 6 days, respectively. Total costs of admissions and mean values of DRG during the 15 year of the study period were € 72,717,232 and € 3,298 respectively. Mean ratio between number of admissions and number of RTRs during the study period was 1.58.

Number of admissions and total number of days required for RTRs increased from 2001 to 2015, however mean and median LOS remained stable. Costs gradually increased during follow-up (*Figure 6*). Mean cost per patient remained stable during the 15 years of the study (7,900±462 €).

Figure 5. *Number of renal transplant recipient admissions during the study period.*

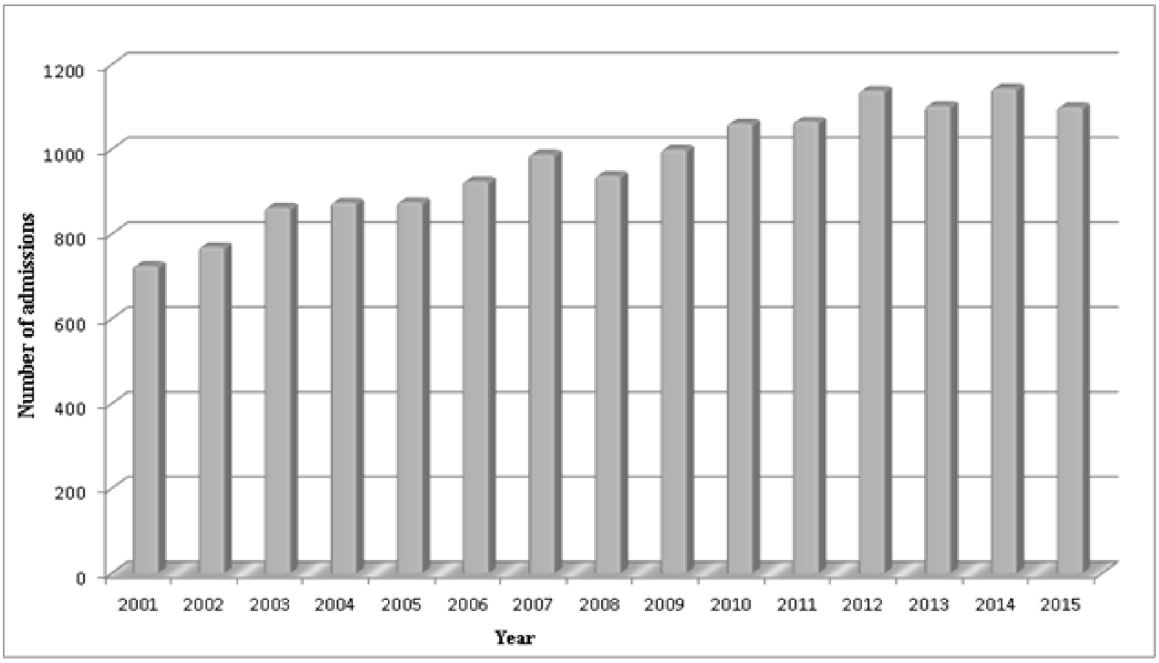


Figure 6. *Costs of renal transplant recipient admissions during the study period*

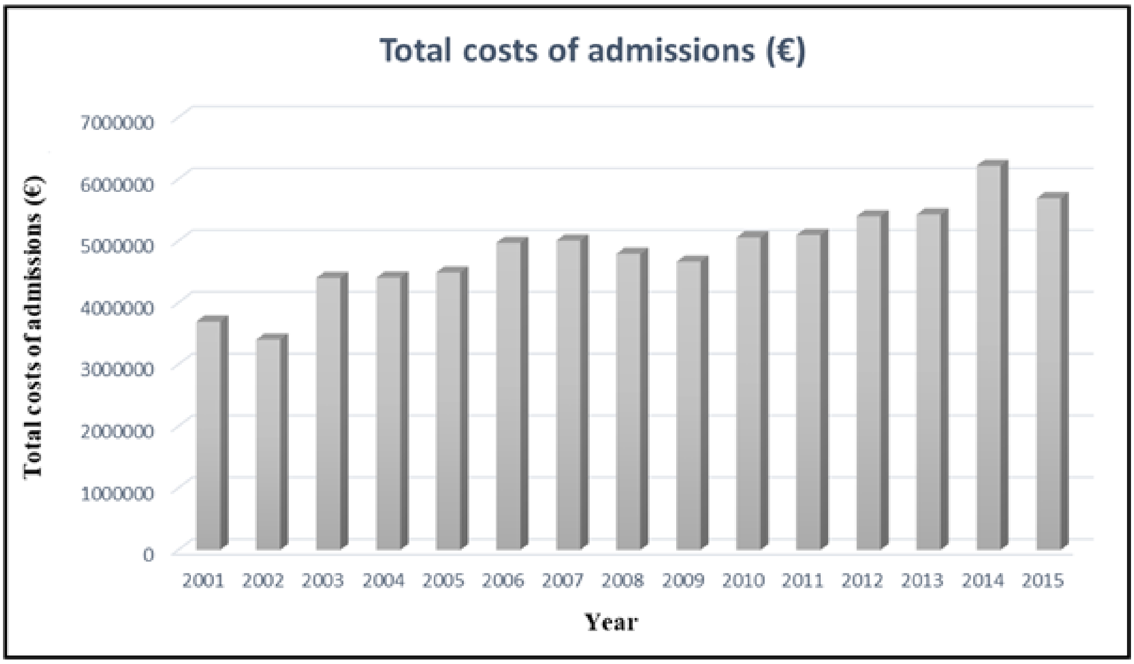


***Table 9**. Number of admissions, number of renal transplant recipients (RTRs), inhabitants of the region Emilia-Romagna (RER) of Italy, rate of admissions, rate of admitted RTRs, length of stay in the hospital (LOS), mean value of diagnosis related groups (DRG) and costs of admissions during the 15-year period of the study.*

Year	Number of admissions (N)	Number of RTRs (N)	RER inhabitants (N)	Rate of admissions (*100,000)	Rate of admitted RTRs (*100,000)	LOS (days)	Mean LOS (days)	Median LOS (days)	Mean values of DRG (€)	Total costs of admissions (€)
2001	724	471	4,037,095	17.93	11.67	6,197	8.6	6	2,686	3,694,494
2002	769	486	4,059,416	18.94	11.97	7,034	9.2	6	2,688	3,404,004
2003	862	544	4,101,324	21.02	13.26	7,177	8.5	5	2,871	4,400,249
2004	874	557	4,151,335	21.05	13.42	7,098	8.3	5	2,881	4,404,496
2005	875	553	4,187,544	20.90	13.21	7,057	8.3	5	3,040	4,490,441
2006	924	567	4,223,585	21.88	13.42	7,056	7.9	5	3,289	4,970,953
2007	987	605	4,275,843	23.08	14.15	7,930	8.3	5	3,310	5,007,249
2008	937	607	4,337,966	21.60	13.99	7,762	8.5	5	3,469	4,791,925
2009	999	642	4,395,606	22.73	14.61	8,242	8.6	5	3,278	4,663,245
2010	1,060	659	4,432,439	23.91	14.87	9,493	9.3	6	3,489	5,058,400
2011	1,065	672	4,459,246	23.88	15.07	9,174	8.9	5	3,491	5,098,514
2012	1,138	698	4,471,104	25.45	15.61	9,379	8.4	5	3,607	5,398,123
2013	1,102	704	4,452,782	24.75	15.81	9,306	8.6	6	3,734	5,426,638
2014	1,143	718	4,457,115	25.64	16.11	10,155	9.1	6	3,909	6,218,851
2015	1,099	714	4,454,393	24.67	16.03	9,906	9.2	6	3,734	5,689,650
Total/Mean	14,558	9,197	4,299,786	22.50	14.21	122,966	8.7	6	3,298	72,717,232

3.4. CONSIDERATIONS ABOUT IMPACT OF HOSPITAL ADMISSIONS SUBSEQUENT TO RENAL TRANSPLANTATION

To the best of our knowledge, this is the first study in which costs of hospital admissions of RTRs after transplantation operation have been analyzed in our country. We could understand that hospital management of this group of patients is complex and skills from multiple health care professionals are needed, RTRs hospital care is not limited to nephrology or renal transplant units but involve multiple specialists, therefore widespread knowledge on follow-up of renal transplantation is required. During the study period, every patient was admitted one and a half times every year, however costs appear to gradually increase in the long term, related to a progressive increase of the number of RTRs, and probably to their mean age. Costs appear to be similar to those reported by other authors, considering the limits due to different study designs.

CKD represents one of the major public health problems in western health care systems. Treatment in its advanced stage is highly expensive, being dialysis and transplantation, the two methods able to replace renal function. Incidence and prevalence of ESRD are increasing worldwide expanding costs of renal replacement therapy [Lysaght MJ 2002; Schieppati A & Remuzzi G 2005]. Patients with ESRD could receive a pre-emptive transplant or begin dialysis (hospital, satellite or home haemodialysis or peritoneal dialysis). Kidneys for transplantation could be obtained from living donor or deceased donor. Transplantation provides a significant health and financial benefit to patients and society.

The average annual costs per health state calculated by health professionals belonging to region Lombardia in Italy in all types of renal transplantation (living donors, donation after brain death and donation after cardiac death) for managing complications in the year of transplant and subsequent years was € 2,597 [Cavallo MC et al 2014]. Similar yearly costs were reported by Sánchez-Escuredo [Sánchez-Escuredo A et al 2015], moreover authors evaluated the annual total cost of kidney transplantation that resulted lower than hemodialysis (€ 29,897 vs € 43,000). The study concluded with an encouragement of kidney transplantation due to the associated economic savings in addition to a better quality of life. Even if renal transplantation is expensive, in the years following the operation, hospital costs could decrease and they are lower than those associated with maintenance dialysis.

Li et al. [Li B et al 2015] evaluated patients who received kidney transplant in England between 2003 and 2006 calculating costs. Authors studied 4,149 incident transplant patients, aged 45.4 years with an average number of comorbidities of 1.56 at baseline, including congestive heart failure, peripheral vascular disease, diabetes, hypertension, myocardial infarction, liver disease, and cerebrovascular disease, conditions that were associated with higher costs. Mean annual inpatients costs over 6 years ranged from £ 4231 (~€ 4,818) during the first year to £ 1145 (~€ 1,304) in the last year. The same authors reported that the increase in mean annual costs associated with comorbidities ranged between £ 264 (~€ 301) and £ 2093 (~€ 2,384) in admitted RTRs [Li B et al 2017].

We are conscious that costs of hospitalizations due to complications in RTRs are highly variable. Ellimoottil et al. [Ellimoottil C et al 2016] recently reported that inpatients costs at hospital level, varied approximately 4-fold for both deceased donor and living donor RTRs. Additionally, authors found no statistical difference between low and very high-cost hospitals with respect to the individual complications of surgical site infections, wound disruption, sepsis, pulmonary embolism and/or deep vein thrombosis, stroke, acute myocardial infarction, pneumonia, prolonged ventilation, general infections, and genitourinary specific complications. Authors identified the following factors as primary sources of hospitalized costs: complications, longer LOS, higher hospital volume and inpatient procedures [Ellimoottil C et al 2016].

In 2015 Kent et al. [Kent S et al 2015] evaluated reliable estimates of the impacts of CKD stage on hospital costs. Their study enrolled 7,246 patients between 2003 and 2006 of whom 70% were recruited in Europe, 18% in Australasia and 12% in North America, aged 63±12 years (64% male). Number of patients on functioning kidney transplant from an earlier annual period were 470 of whom 9 were on CKD stage 1-3B, 126 on CKD stage 4 and 335 on CKD stage 5 not on dialysis. Annual hospital care costs in absence of diabetes and cardiovascular complications were £ 1,148 (~€ 1,307). Non-fatal major vascular events increased annual costs in the year of event by £4,350 (~€ 4,954) for patients not on dialysis and were associated with increased costs though to a lesser extent, in the subsequent year [Kent S et al BMC Nephrol 2015].

Chaumard et al. [Chaumard N et al 2008] calculated daily cost of hospitalization corresponded to direct charges, including medical expenses, boarding expenses, staff pay, laundry, and maintenance as well as induced charges of medical/technical and logistic costs, including organizational costs. Daily pharmaceutical expenses were defined for each unit involved in the operation of transplantation. At the time of transplantation mean daily cost was € 877, and daily cost attributed to nephrology was € 405 [Chaumard N et al 2008].

Our study has several limitations. First, it is a retrospective study analyzing an administrative dataset, so that potentially important parameters such as disease severity, including the degree of renal impairment, were not available. Second, in this study we analyzed all records and not each single patient, we also excluded pharmaceutical expenses that in these patients could be very high. Third, ICD-9-CM codes for renal transplantation have not been validated and studies based on ICD-9-CM codes are exposed to a possible codification bias, even if it has been shown that risk models developed using administrative data had good performance in predicting emergency hospital admissions [Wallace E et al 2014]. Fourth, elective and emergency admissions were not analyzed separately. Moreover, out-of-hospital follow-up expenses were not taken into consideration due to the fact that DRG considered only costs focused on hospital admissions. On the other hand, DRG like any form of payment, could induce un-desirable behavior by providers. Adverse effects that have been widely recognized such as selection of patients, up-coding of severity levels, premature discharge of patients, could not be considered. Moreover, DRG payment could foster development of hospital activity beyond what is medically necessary, does not encourage improvement in care pathways, and might not be optimal for paying for patients with chronic diseases. We are conscious that hospital costs calculated in this study could be of limited value due to limited generalizability to different Italian regions and also to different countries, however they appear similar to those published by different authors in different countries, also considering all different study designs. We analyzed mean costs per admission and we did not take into consideration reasons for admission, because our aim was to only evaluate costs related to admissions after transplantation using administrative data. Unfortunately, the true costs could be very different, therefore it is necessary to plan a nations survey based on a national registry in order to evaluate precisely the correct cost effectiveness ratio. However, this study also has some strengths. It is the first large scale study, accounting for more than 10,000 hospital admissions, recorded by an established database, used in recent studies for investigating IHM in renal transplant recipients [Fabbian F et al 2018; Fabbian F et al 2016 (b)]. Finally, we did not take into consideration late event needing surgical re-intervention including minimally invasive approach [Manassero F 2017].

Our data add knowledge to a very complex clinical condition undergoing a continuous development of surgical techniques [Territo A et al 2017; Özkaptan O et al 2018], and we conclude that considering the complexity related to RTRs management, costs due to admissions of RTRs appeared to gradually increase in the long term probably due to the increasing number of admissions and increasing mean age of admitted RTRs.

V. DISCUSSION

1. PERSONAL EXPERIENCE IN AN UNIVERSITY HOSPITAL LOCATED IN NORTHEAST OF ITALY

In 2015 we carried out a study in order to evaluate the possible relationship between WE effect, IHM, and gender in a large sample of consecutive patients admitted to our hospital, independently from reason of admission, ward of destination, and clinical conditions at the time of admission. We analyzed age, sex, CCI calculated on the basis of ICD-9-CM. Time of admission and day of the week of each admission were classified into WE (from midnight of Friday to midnight of Sunday) and weekdays (WD) (Monday to Friday). The 9-main national festive days in Italy (January 1, April 25, May 1, June 2, August 15, November 2, December 8, December 25 and 26), when occurring on WD, were considered as WE. IHM was assumed as primary end-point. The analysis was limited to IHM and restricted to 30 days from hospitalization. During the 14-year study period, 411,588 hospital admissions in 208,010 patients (90% from the ED) were considered. Males were 47% (mean age, 53.3±27.1 years) and females were 53% (mean age, 53.6±26.4 years). Of these patients, 14,006 (6.7%) died during hospitalization. As for patients admitted during WE or WD, age (53.5±28.6 vs 53.5±26.3 years) and prevalence of females were similar (17.7% vs 17.2%), whereas CCI was significantly higher (1.16 ±1.90 vs 1.13±1.89; $p<0.001$) in subjects admitted during WE. Univariate analysis showed that IHM was related to age (75.1±14.9 vs 52.7±26.7; $p<0.001$), CCI (3.05±2.86 vs 1.07±1.81; $p<0.001$), WE admission (WE 4.7% vs WD3.1%; $p<0.001$), and male sex (3.9% vs 3%; $p<0.001$). Logistic regression analysis revealed an independent association between IHM and age (OR, 1.052; 95%CI, 1.051-1.053; $p<0.001$), male sex (OR, 1.251; 95% CI, 1.208-1.295; $p<0.001$), admission during WE (OR, 1.413; 95% CI, 1.356-1.472; $p<0.001$), and CCI (OR, 1.276; 95% CI, 1.268-1.284; $p<0.001$). A further separate analysis was also performed on the subgroup of subjects admitted during WE (n = 71,965, 33,380 males, 46.4%, mean age 53±28.7 years; 38,585 females, 53.6%, mean age 53.9±28.6), which showed that IHM group had higher age (76 ±15.2 vs 52.4 ± 28.7 years; $p<0.001$), higher prevalence of male sex (5.2% vs 4.3%; $p<0.001$), and higher CCI (2.91±2.74 vs 1.08 ± 1.81; $p<0.001$) than survivors. Multivariate analysis confirmed that, in WE patients, IHM was independently related to age, male sex, and CCI. The study showed that, in patients admitted to the hospital during WE, IHM was higher especially in male subjects. We wanted to verify the hypothesis of different outcome in males and females, and our results showed that gender seemed to be an important risk factor for IHM, independently from age and CCI. Although no definite conclusions could be drawn by a single study, this topic should deserve further confirmations in different health care settings, to identify possible causes and provide adequate measures since the first step of presentation to the ED [De Giorgi A et al 2015].

In 2015 our group investigated the relationship between diagnosis of urinary tract infections (UTIs) based on ICD-9-CM codes and IHM in a consecutive cohort of patients admitted to University Hospital St. Anna, in order to evaluate the odds of age, gender, type of cultural organism, and sepsis as life-threatening factors. All patients in whom an ICD-9-CM code of UTIs were included, independently of site of infection, symptoms and department of admission, and systemic complications, such as sepsis, were also taken into account. Moreover, CCI based on ICD-9-CM was also calculated and IHM was our main outcome. The ICD-9-CM codes used to define UTIs were 112.2, 098.xx, 599.0 associated with 0.41.xx. The total sample consisted of 2,266 patients (73.7% females), with a mean age of 81.7±7.5 years. Sepsis developed in 116 (5.1%), and fatal outcome occurred in 84 (3.7%). More of 70 percent of UTIs were due to Escherichia (E) coli. Deceased patients had lower prevalence of UTIs due to E. coli (53.6 vs 71.7%, p<0.001) and higher prevalence of UTIs due to Pseudomonas (P) aeruginosa (19 vs 7.1%, p<0.001) infections. Again, they were more likely to have sepsis (31% vs 4.1%, p<0.001) and had higher CCI (2.81±2.43 vs 2.21±2.04, p=0.011). Logistic regression analysis showed that IHM was independently associated, in decreasing ORs order, with: sepsis (OR 10.3; 95%CI 6.113-17.460, p<0.001), P. aeruginosa infection (OR 2.541; 95%CI 1.422-4.543, p=0.002), female gender (OR 2.324; 95%CI 1.480-3.650, p<0.001), CCI (OR 1.103; 95%CI 1.005-1.210, p=0.038), age (OR 1.034; 95%CI 1.002-1.066, p=0.036), and E. coli infection (OR 0.5; 95%CI 0.320-0.780, p=0.002). Interestingly, when analyzing the population as a whole, female gender exhibited the same high OR than Pseudomonas (P) aeruginosa, and comorbidity was significantly associated with IHM. When the two subgroups by gender were analysed separately, comorbidity disappeared from significant factor, whereas age remained significant only for males. The presence of sepsis always exhibited the highest OR (10.052, 95%CI 5.645-18.259, p<0.001), even if ORs were about 2.5-fold higher in males (15.459, 95%CI 6.912-34.574 vs. 3.387, 95% CI 3.324-14.397, respectively, p<0.001). The study, conducted in an area of North-East of Italy on a large series of consecutive admissions, and representative of the geriatric population of our Region and our Country, gives further confirmation that gender and comorbidities are risk factors for IHM in subjects with UTIs. In patients admitted in a hospital of North-Eastern area of Italy, a higher IHM was mainly related to female gender, comorbidities (expressed by CCI), and age, even if total mortality was remarkably lower compared to that reported in Literature. In particular, logistic regression analysis showed that IHM was independently associated with female gender (OR 2.32). In a recent study on a large cohort of more than 3,900 ICU patients (36.5% females) in the North-Western area of Italy (Region of Piedmont), ICU mortality was similar in men and women in the whole cohort, but female gender was independently associated with a higher risk of ICU death in patients with severe sepsis (OR 2.33) [Sakr Y et al 2013]. These results, apparently contradictory to the literature findings of a better response of female gender to sepsis, could be explained by the older age of patients enrolled in the Italian studies (66±16 years in Piedmont, 81.7±7.5 years in Emilia-Romagna), largely beyond the protective effect observed in the premenopausal age. Moreover, this significantly higher age implies the presence of important comorbidities, and it is known that the CCI has a great importance as a predictive factor for mortality [Green JE et al 2014]. The possibility to identify predictors of negative outcome in elderly patients with UTIs could help physicians in the clinical decision making process, especially in a period of paucity of resources [Fabbian F et al J 2015 (b)].

In 2016 our group performed a study, based on DHR, in order to evaluate the relationship between the presence of renal dysfunction, both chronic kidney disease (CKD) and acute kidney injury (AKI), and IHM in patients admitted to the Internal Medicine wards of our hospital because of severe chronic obstructive pulmonary disease (COPD) exacerbation. All patient admitted in internal medicine department of our hospital with diagnosis of COPD exacerbation (ICD-9-CM 491.21) were included in the study. Subjects with different COPD-related diagnosis such as 491.xx (chronic bronchitis), 492.xx (emphysema), 496.xx (chronic airway obstruction, not elsewhere classified) were excluded. Renal dysfunction ICD-9-CM codes used were 585.xx for CKD and 584.xx for AKI. Subjects on renal replacement therapy were excluded. Hypertension was identified by ICD-9-CM codes 401-405. ICD-9-CM codes necessary to calculate CCI were evaluated in order to take into account comorbidity. For score calculation, the following diseases were considered: hypertension, obesity, diabetes mellitus, cardiac and peripheral vascular diseases, cerebrovascular disease, hematological and solid neoplasms, liver disease. The CCI was corrected removing the effect of kidney dysfunction. Age and sex were the other variables considered and length of hospital stay (LOS) was calculated. In patients with multiple admissions during the study period, only the last one was considered being IHM our main outcome. During the study period 411,588 patients were admitted of whom 7,073 (1.7%) were hospitalized because of COPD exacerbation; they were more frequently male (56.9%), mean age was 76.7±9.8 years, and LOS was 10.3±11.2 days (median 8 days). CKD diagnosis was present in 771 patients (10.9%), while AKI was diagnosed in 354 cases (5%). CCI corrected for renal dysfunction was 2.30±1.65, and 554 patients (7.8%) died during hospitalization. Hypertension was diagnosed in 3,147 subjects (44.5%) and female patients were older than male ones (77.7±10.6 vs 75.9±9.1 years, $p<0.001$). Moreover, only 9 patients (2.5%) admitted because of COPD exacerbation with AKI underwent dialysis treatment. Deceased patients were older (81.2±7.9 vs 76.3±9.9 years, $p<0.001$), had higher CCI (2.61±2.21 vs 2.28±1.62, $p=0.001$), longer LOS (11.1±15.1 vs 10.3±10.8 days, $p=0.001$) and had higher prevalence of AKI during hospitalization (16.6% vs 4%, $p<0.001$) than survivors. Multivariate logistic regression analysis showed an independent association of IHM with age (OR 1.063; 95%C.I. 1.050-1.075, $p<0.001$), male sex (OR 1.229; 95%C.I. 1.016-1.486, $p=0.033$), logCCI (OR 2.051; 95%C.I. 1.419-2.964, $p<0.001$) and AKI (OR 3.849; 95% C.I. 2.874-5.155, $p<0.001$). In our study, renal dysfunction was a frequent complication of patients admitted to the hospital for a severe COPD exacerbation, however the presence of CKD was not related to IHM, while the presence of AKI is an important negative prognostic risk factor. AKI represents a very important predictive factor of IHM in older male patients admitted for COPD exacerbation especially if they show different comorbidities. Greater awareness is needed because AKI represents a condition on which it's possible to act aiming to reduce IHM. So, it's important an accurate follow-up of renal function in older patients hospitalized for COPD exacerbation, especially checking medical treatment. This approach could improve firstly patient's prognosis and secondly reduce health care costs [Fabbian F et al 2016 (a)].

In 2016, we evaluated the relationship between IHM and pulmonary embolism (PE), comorbidities, and possible sex differences in a consecutive cohort of patients admitted to our hospital with Alzheimer disease (AD; ICD-9-CM code 331.0). The code 415.1, as main diagnosis, was used for diagnosis of acute PE. Comorbidity was evaluated with CCI. Total sample consisted of 8,201 patients (63.9% women; mean age, 79.7±12 years). Mean CCI adjusted for age and dementia was 1.99±1.82 (median, 2; range, 0-16), and 631 subjects (7.7%) died during hospitalization. Pulmonary embolism was diagnosed in 83 patients (1%), with 17 (20.5%) fatal cases. Deceased patients were older (80.7±11.7 vs 79.7±12 years, p=0.041), more frequently men (10.2% vs 6.3%, p=0.001), and more likely to have pulmonary embolism (PE) (2.7% vs 0.9%, p<0.001). Logistic regression analysis showed that IHM was significantly associated with PE, male sex, and age. We showed a sex effect because women were more affected by AD, but fatal PEs were more likely to occur in men [Fabbian F et al 2016].

2. PERSONAL EXPERIENCE USING DATA FROM REGIONAL ADMINISTRATIVE DATABASES

In 2013, we compared IHM for myocardial infarction (MI) in patients with chronic kidney disease (CKD), end-stage renal disease (ESRD), and in subjects without renal dysfunction living in the Emilia-Romagna region of Italy. The ICD-9-CM codes used to define CKD and dialysis were 585.*, 586 and V45.1, V56.* respectively. Comorbidity was evaluated with CCI, and diagnoses of hypertension, obesity, diabetes mellitus, heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease and malignancy were also considered per se, as comorbidity components. Since the original CCI incorporates also CKD, to limit the possible influencing effects of renal dysfunction, the index modified excluding CKD was calculated. From 1 January 1999 to 31 December 2009, 82,785 cases of acute MI were recorded in patients without renal dysfunction. Of these, 50,804 events occurred in males (mean age 68±13 years) and 31,981 in females (77±12 years, comparison vs males p<0.001). Moreover, 4,495 cases occurred in patients with CKD, (2,808 in males, age 78±10 years, and 1,687 in females, age 83±9 years, comparison vs males p<0.001); and 734 cases in patients with ESRD, (493 in males, age 72±10 years, and 241 in females, age 74±10 years, comparison vs males p=0.001). The percentage of patients admitted with MI and died during hospitalization was higher in ESRD and CKD patients than in subjects without renal dysfunction (38.3 vs. 16.5 vs. 14% respectively; p<0.001). During the study period, IHM showed a two-fold increase in CKD and ESRD patients, although in the latter group the difference was not statistically significant. Factors independently associated with IHM were age (OR 1.077, 95% CI 1.075-1.080, p<0.001), CCI excluding CKD

(OR 1.101, 95% CI 1.069-1.134, p<0.001), cerebrovascular disease (OR 1.450, 95%CI 1.349-1.557, p<0.001) malignancy (OR 1.234, 95%CI 1.153-1.320, p<0.001), and ESRD (OR 4.137, 95%CI 3.511-4.875, p<0.001). We concluded that at least according to ICD9-CM codification data, patients with ESRD on dialysis living in a North-Eastern region of Italy, during a follow-up longer than 10 years, had a significantly higher MI mortality compared with subjects without renal dysfunction [Fabbian F et al 2013 (b)].
In the same year, our group conducted a study aiming at comparing PE mortality in hospitalized patients with and without CKD and ESRD, in order to evaluate the impact of renal dysfunction on short-term mortality. The criteria for inclusion in the analysis were: emergency admission and acute PE and pulmonary infarction as the main diagnosis (415.1 ICD-9-CM). On the other hand, cases with codes: 415.11 – Iatrogenic PE and infarction, 415.19 – Other, 639.6 – PE complicating abortion, 639.6 – Complications of ectopic or molar pregnancies, and 673.0-673.8 – PE complicating pregnancy, childbirth or the puerperium were excluded. Only admissions directly related to PE were extracted from the database. Since we focused only the hospital admissions for a first event of PE, all successive admissions secondary to PE relapse were excluded. The ICD-9-CM codes used to define CKD and dialysis were 585.*, 586 and V45.1, V56.*, respectively. Moreover, ICD-9-CM codes for immobilization, dementia, sepsis, skeletal fractures, hypertension, diabetes mellitus, heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, pneumonia, and malignancy were also collected in order to evaluate comorbidity. From January 1, 1999 to December 31, 2009, 24,690 cases of PE (first event) were recorded. Of these, 10,517 events occurred in males (42.6%, 72.2±13.9 years) and 14,173 in females (57.4%, 77.0±13.4 years, comparison vs males, p <0.001); 5,813 (23.5%) subjects died during admission because of PE. IHM for PE was not different in the three groups of patients (23.6% vs 24% vs 18% p=ns). In subjects with CKD and in those with ESRD only skeletal fractures and pneumonia, respectively, were associated with IHM for PE. IHM or PE decreased from 1999 to 2009 in all the three groups of patients. IHM for PE was independently associated with age (OR 1.045, 95%CI 1.042-1.048, p<0.001), female sex (OR 1.322, 95%CI 1.242-1.406, p<0.001), hypertension (OR 1.096, 95%CI 1.019-1.178, p=0.013), diabetes mellitus (OR 1.120, 95%CI 1.001-1.253, p=0.049), dementia (OR 1.171, 95%CI 1.020-1.346, p=0.025), peripheral vascular disease (OR 1.349, 95%CI 1.057-1.720, p=0.016) and malignancy (OR 1.065, 95%CI 1.016-1.116, p=0.008). In contrast, neither CKD nor ESRD resulted

to be associated with mortality after hospital admission for PE. We concluded that, although cardiovascular risk factors play a major role in renal function decline [Mangione F & Dal Canton A 2011], it is somewhat difficult to ascertain an independent role of CKD as a cause of PE. As a matter of fact, major cardiovascular risk factors such as hypertension, atherosclerosis, and diabetes, are main causes of CKD. Moreover, the common knowledge that arterial and venous thrombosis are separate disease entities has been challenged by recent evidence demonstrating that the two conditions share common risk factors [Di Minno MND et al 2012]. Our group confirmed an increased IHM for MI in patients with renal dysfunction [Fabbian F et al 2013 (b)]. On the contrary, at least according to ICD-9-CM codification data, in this region of Italy CKD or ESRD on dialysis do not seem to increase the risk of IHM in patients admitted for PE. Further studies are needed to evaluate the clinical severity of PE events in patients with renal failure, and the possible impact of different therapeutic strategies, i.e. anticoagulants and antiplatelet agents, on the mortality of this special population [Fabbian F et al 2013 (a)].

In 2014 we carried out a study, performed on the administrative database of the Emilia Romagna region of Italy, in order to evaluate a relationship between renal dysfunction, IHM and stroke. The criteria for inclusion in the analysis were (a) emergency admission and (b) ICD-9-CM code for stroke (430–431–432–433– 434) as the principal diagnosis. Stroke was further classified into ischemic stroke (433–434), and hemorrhagic stroke (430–431– 432). Since we focus only on first events of stroke, all successive readmissions with the same diagnosis were excluded. As for the definition of renal dysfunction, CKD and dialysis, the ICD-9-CM codes were 585.*, 586 and V45.1, V56.*, respectively. IHM for stroke (total events), and for ischemic and hemorrhagic, separately, were chosen as the outcome indicators. Comorbidity was evaluated with CCI. Moreover, due to its importance as a risk factor, ICD-9-CM code for atrial fibrillation (AF) (427.31) was also considered. Since the original CCI incorporates also CKD, to limit a possible overestimation bias of renal dysfunction, we calculated such index excluding CKD. From January 1, 1999 to December 31, 2009, 186,219 admissions for a first episode of stroke were recorded. Of these, 89,962 events occurred in males (48.3%) and 96,257 in females (51.7%); 22,055 (11.8%) patients died during hospitalization. IHM in patients with no renal dysfunction (n=183,776; 98.7%) was 11.6%, and it was significantly higher in patients with CKD (n=1,624; 0.9%), and with ESRD (n=819; 0.4%): 33.9 and 30.6% ($p<0.001$), respectively. Ischemic strokes were

154,026 (82.7%), hemorrhagic events were 32,189 (12.3%). Fatal cases during hospitalization occurred in 12,997 (8.4%) and 9,057 (28.1%), respectively. The results of multivariable logistic regression analysis showed that: (a) IHM for stroke (total events) was independently associated with: age (OR 1.001 [95%CI 1.000-1.003], $p = 0.017$), CKD (OR 3.715 [3.346-4.125], $p < 0.0001$), ESRD (OR 3.413 [2.938-3.964], $p < 0.0001$), AF (OR 1.611 [1.551-1.673], $p < 0.0001$) and CCI (OR 1.078 [1.062-1.094, $p < 0.0001$); (b) IHM for ischemic stroke was independently associated with: CKD (OR 4.052 [3.592-4.571], $p < 0.0001$), ESRD (OR 3.806 [3.147-4.604], $p < 0.0001$), AF (OR 2.198 [2.105-2.296], $p < 0.0001$) and CCI (OR 1.168 [1.148-1.189], $p < 0.0001$); (c) IHM for hemorrhagic stroke was independently associated with: CKD (OR 4.235 [3.279-5.469], $p < 0.0001$), ESRD (OR 2.099 [1.621-2.717], $p < 0.0001$) and AF (OR 1.229 [1.127-1.340], $p < 0.0001$). We underlined the independent role of CKD as a cause of cardiovascular events is difficult to be established, due to the tight relationship between cardiovascular risk factors and renal function decline. All the major cardiovascular risk factors, in fact, such as hypertension, atherosclerosis, and diabetes, are considered themselves as causes of CKD. However, this study shows that renal dysfunction is associated with mortality from stroke, with significantly higher ORs than those of other established risk factors, such as age, comorbidities and AF. Renal dysfunction appears to be independently associated with IHM due to stroke, both ischemic and hemorrhagic, and information on kidney function is routinely available to clinicians at hospital presentation, and its evaluation could suggest the burden of vascular damage [Fabbian F et al 2014].

In 2016, we conducted a retrospective study was to investigate the risk factors for IHM and hospitalization attributable to cardiovascular disease (CVD), taking into consideration non-immunologic comorbidity evaluated on the basis of ICD-9-CM codification, in a large sample of renal transplant recipients (RTRs).

The study included all RTRs, considering all cases of admission because of any complications recorded from 2001 to 2013. The inclusion criterion was the presence, as a main discharge diagnosis, of any cardiovascular event (CVE) cerebral, cardiac and peripheral such as myocardial infarction, stroke, congestive heart failure, and any intervention for aortic abdominal aneurysm and for peripheral re-vascularization, according to ICD-9-CM. The EI was calculated taking into account ICD-9-CM codes, and IHM was also recorded. The ICD-9-CM codes used to define RTRs was V420. The ICD-9-CM classified chronic kidney disease (CKD) based on severity. The severity of

CKD is designated by stages I-V. The code V420 defined the diagnosis of kidney transplant status or kidney replaced by transplant We considered as main outcomes: a) IHM, considering fatal cases (death during hospitalization) and non-fatal cases (patient discharged alive); b) admission due to major cardiovascular events (ICD-9-CM 014, 015, 016, 078, 121, 122, 123, 124, 125, 127, 129, 130, 140, 524, 559); c) both a+b. The EI was calculated for evaluation of non-immunologic comorbidity [Elixhauser A et al 1998]. The EI is able to identify the following most important limitations to individual wellness, such as paralysis, drug abuse, metastatic cancer, peptic ulcer disease excluding bleeding, obesity, alcohol abuse, peripheral vascular disorders, valvular disease, other neurological disorders and rheumatoid arthritis/collagen disorders. For ICD-9-CM codes for calculating the EI we referred to Quan et al. [Quan H, et al 2005].

During the examined period, a total of 9,063 admissions in 3648 RTRs were recorded, i.e. about 2.5 admissions per patient. 1,945 patients were males (53.3%) and 1703 females (46.7%), and the mean age was 52.9±13.1 years. The non-immunological impaired status of the RTRs, examined by the EI, was 3.88±4.29 (median value 5). EI≥10 was calculated in 926 subjects (10.2%). During the 14-year follow-up period, IHM for any cause was 3.2% (n=117), and admissions due to CVEs were 527 (5.8%). IHM and/or CVEs were recorded in 626 of the admissions analyzed (6.9%) and were ascribed to older patients with higher comorbidity. Duration of hospitalization was longer in deceased patients than in survivors (20.8±20.1vs 9.5±11.9 days, $p<0.001$). Thirty-three out of 117 deceased RTRs underwent major surgical procedures (8 gastrointestinal, 8 osteoarticular, 6 cardiovascular, 6 other interventions), and 35 out of 117 deceased RTRs underwent dialysis treatment, being the latter performed in a higher percentage of patients in the deceased grout than in survivors (29.9 vs. 9%, $p<0.001$). Age and comorbidity were independently associated with CVEs, IHM and the combined outcome. Moreover, male gender was independently associated with IHM and combined outcome, but not with CVEs. We concluded that evaluation of non-immunological comorbidity is important in RTRs, and identification of high risk patients for major clinical events could improve outcome. Moreover, comorbidity could be even more important in CKD patients who are waiting for a kidney transplant [Fabbian F et al 2016 (b)].

In 2017 we evaluated the possible relationship between day of week hospital admissions for cardiovascular disease, IHM, and comorbidities in RTRs. The study included all RTRs admitted for any cause recorded during the period of study. The inclusion criteria were the association between ICD-9-CM code V420 - diagnosis of kidney transplant status or kidney replaced by transplant - and codes of any major cardiovascular event (CVE), e.g. myocardial infarction, stroke, aortic aneurysm, congestive heart failure, and related interventions. The EI index, was calculated considering ICD-9-CM codes; the IHM was also recorded. As for temporal definition, midnight Friday to midnight Sunday was considered as week-end (WE), while all the other days were assumed as weekdays (WD). We analyzed: a) IHM, considering fatal cases (death during hospitalization) and non-fatal cases (patient discharged alive); b) admission due to major CVEs (ICD-9-CM codes: 014, 015, 016, 078, 121, 122, 123, 124, 125, 127, 129, 130, 140, 524, 559); c) both a+b in RTRs admitted during WE and WD. The EI was calculated for evaluation of non-immunologic comorbidity. Such a score can identify the most important limitations to individual wellness, such as paralysis, drug abuse, metastatic cancer, peptic ulcer disease excluding bleeding, obesity, alcohol abuse, peripheral vascular disorders, valvular disease, other neurological disorders and rheumatoid arthritis/collagen disorders. The EI was calculated considering ICD-9-CM codes according to Quan et al. [Quan H et al. 2005]. LOS was also evaluated. Out of 9,063 hospital admissions related to 3,648 RTRs, 1,491 (16.5%) were recorded during WE. The mean age of the entire population was 53±13 years, and in 62.9% of cases, admissions involved male patients. LOS was 9.7±12.1 days and median EI was 5 (range -7;31). Age, sex distribution, prevalence of deceased patients and CVEs and EI was similar in patients admitted during WD and WE, whereas duration of hospitalization was longer in the latter group (10.5±10.8 vs. 9.8±12.3 days, $p<0.001$). Logistic regression analysis evaluating the variable independently associated with WE admissions including age, sex, IHM, CVEs, comorbidity score and duration of hospitalization as independent variables showed that only LOS was related to WE admissions (OR: 1.594, CI 1.385-1.833, $p<0.001$).

We concluded that RTRs are not exposed to higher risk of adverse outcome in the case of WE admissions, suggesting that our regional health organization could ensure a sufficient level of efficiency avoiding major adverse outcome in this selected population, therefore our hospital organization could be one of the reasons for the lack of WE effect among RTRs. On the other hand, we found that WE admissions were characterized by an increased duration of hospitalization, suggesting that further efforts are needed in order to reduce the burden of hospital costs [Manfredini R et al 2017].

In 2017, we assessed how CKD contributes to overall mortality in a population-based cohort of patients living in the region Veneto of Italy and discharged with a diagnosis of COPD, taking into account the burden of other comorbidities. All residents in the Veneto region aged ≥45 years discharged from January 1, 2008, to December 31, 2010 with a diagnosis of chronic bronchitis (ICD9-CM code 491), emphysema (492), another COPD (496) were identified. Subjects dying during the hospitalization were excluded. Severity of COPD was approximated by the following criteria derived from claims data: a hospital diagnosis or an exemption from medical charges due to respiratory failure; previous hospitalizations for COPD. A three-level score was attributed to subjects with none, one, or both of the above criteria. To identify comorbidities, the modified version of the CCI adapted to ICD-9CM codes was adopted based on diseases reported in the index hospitalization, and in all hospital admissions in the previous three years. Whenever possible, single comorbidities were identified also based on exemptions form medical charges; e.g. study subjects were classified as affected by CKD in the presence of discharge diagnoses identifying CKD according to the ICD9-CM 582, 583, 585, 586, 588, and/or in the presence of an exemption from medical charges due to renal failure after certification by a specialist. Criteria for identifying patients with ischemic heart disease, heart failure, cerebrovascular disorders, and peripheral arterial disease were expanded according to previous studies carried out in the Veneto region [Ferroni E et al 2016]. The CCI was computed after the exclusion of COPD and CKD, the focus of the present study. Subjects discharged with a diagnosis of COPD were followed-up by linkage with population records to assess vital status and emigration out of the region, and with the regional archive of causes of deaths for the period from 2008 to 2013. Each subject was followed from the index hospital discharge either until death, or emigration outside the study area, or 31 December 2013, whichever came first. In the Veneto region, the cause of death is coded according to the International Classification of Diseases-10th Edition (ICD-10); it is selected from all the diseases mentioned in the death certificate by means of the Automated Classification of Medical Entities, a computer program developed by the US National Center for Health Statistics to standardize mortality statistics [Lu TH et al 2010]. Overall 27,272 patients were enrolled in the study cohort. Of these, 1.0% were censored during follow-up because they emigrated out of the study area, or died without the possibility of death certificate retrieval, or anyway were no more traceable in population records. Only 39.2% of patients were still alive at the end of a median follow-up of 37 months (17 months for patients dead and 56 months for those alive at the end of follow-up). The age distribution was shifted toward old age classes: 43% of COPD patients were aged 75-84 years, and 25% ≥85 years. Median age was 79 years (interquartile range 73-85). About 60% of patients were males, and 1 out of 3 could be classified as affected by severe/very severe COPD according to the adopted score. Most patients presented with ≥1 comorbidities. The most frequent diseases, tracked in at least 10-20% of the study population, were heart failure, diabetes, neoplasms, cerebrovascular diseases, and CKD. The prevalence of comorbidities increased with age, and levelled off in the very elderly. The observed survival for the whole cohort was 75%, 52%, and 37% at 1, 3, and 5 years of follow-up, respectively. The most frequent causes of death among 16,288 decedents were circulatory disorders (mostly ischemic and other heart diseases), followed by respiratory diseases (mostly COPD, but also respiratory infections, respiratory failure, other and unspecified respiratory disorders) and cancer. Survival was lower in patients affected by CKD; however these latter patients were older than other study subjects and more frequently affected by comorbidities such as heart failure (46%), diabetes (36%), ischemic heart disease (15%), and peripheral arterial disease (12%). When determinants of survival were assessed by means of Cox regression adjusted by age, gender, and severity score of COPD, the presence of CKD as well as of other comorbidities summarized by the modified CCI were significant risk factors for mortality. Results were confirmed if analyses were restricted to patients aged <85 years. We concluded that overall survival of COPD patients was heavily affected by the presence of comorbidities, namely CKD. The analysis of claim data allowed to investigate long-term prognosis in a large population representative of everyday practice. These data could help health care providers in optimizing interventions and resource allocation given the increase in healthcare costs associated with multiple comorbidities [Fedeli U et al 2017].

In 2018, we investigated the relationship between cancer, non-immunologic comorbidity, estimated on the basis of ICD-9-CM codification, gender and IHM in a large sample of RTRs. The study included only RTRs, considering all cases of admission because of any complications recorded from 2001 to 2013. The inclusion criterion was the identification of the ICD-9-CM code V420. ICD-9-CM codes were used to identify all different types of cancers, and to calculate the EI. Neoplasms were grouped in skin cancers (SC, including melanoma), solid organ cancers (SOC), and post-transplant lymphoproliferative disorders (PTLD). In order to avoid overestimation, EI was corrected with the exclusion of the diagnosis of cancer from the index calculation, so obtaining a corrected index (cEI), and according with codification algorhythms for defining comorbidities, SC were identified by codes 172.x-173.x, SOC by codes 140-172.x, 174.x-195.x, 196.x-199.x, and PTLD by codes 200.x-202.x, 203.0, 238.6 [Quan H et 2005]. The total sample consisted of 9,063 admissions related to 3,648 patients, with 117 deaths (3.2%). The mean age was 52.9±13.1 years. Admissions in male patients were 5,703 (62.9%). Cancers were reported in 580 admissions (6.4%), and mean cEI was 3.5±3.4. SC were recorded in 103 admissions (1.1%), PTLD in 107 admissions (1.1%) and SOC in 370 admissions (4.1%). Deceased RTRs were more likely to be male (75.2 vs. 62.8%, p=0.006), to be older (61.6±10.2 vs. 52.8±13.1 years, p<0.001), to show higher cEI (6.1±5.9 vs. 3.4±3.9, p<0.001), to have higher prevalence of cancer (35 vs. 6%, p<0.001), PTLD (7.7 vs. 1.1%, p<0.001), and SOC (20 vs. 3.9%, p<0.001) than survivors. On the contrary, prevalence of SC was not different in the two groups of RTRs (2.6 vs. 1.1%, p=ns). IHM was independently associated (in decreasing order) with PTLD (OR 12.431, 95%CI 5.834-26.489, p<0.001), SOC (OR 6.804, 95%CI 4.323-10.707, p<0.001), female gender (OR 1.633, 95%CI 1.057-2.523, p=0.006), cEI (OR 1.106, 95%CI 1.068-1.145, p<0.001), and age (OR 1.049, 95%CI 1.031-1.068, p<0.001). In conclusion, RTRs are exposed to the risk of IHM related to occurrence of malignancies. However, this risk involves not only RTRs but also for other organ transplants. Recent data from the Taiwan National Health Insurance Research Database, analyzed 5,396 cases, comprising 801 heart, 2,847 kidney, and 1,748 liver transplant recipients between 2001 and 2012 [Lee KF et al 2016]. Compared with the general population, the risk of cancer increased 3.8-fold after heart transplantation, 4.1-fold after kidney transplantation and 4.6-fold after liver transplantation. Interestingly, differences by gender were found in types of cancer: male recipients had an increased risk of cancers of the head and neck and liver, and female kidney recipients had a significant risk of bladder and kidney cancer [Lee KF et al 2016]. Data from the United States (229,300 U.S. solid organ transplant recipients linked with 15 stage/regional cancer registries (1987-2012), showed that among recipients of different organs, kidney recipients had the highest occurrence of thyroid cancer (Risk Ratio – RR = 1.26, 95% CI 1.03-1.53), even if post-transplantation diagnosis of thyroid cancer was associated with modestly increased risk of death (Hazard Ratio – HR = 1.33, 95% CI 1.02-1.73) [Kitahara CM et al 2017].

In this study focused on cancer-related deaths, female gender exhibited an even stronger association with IHM (OR 1.66) than comorbidities and age. Interesting data, although regarding to a small population, come from a Korean study on 248 kidney transplant patients who underwent a colonoscopy (1996 to 2008) [Kwon JH et al 2015]. Advanced colonic neoplasms was found in 8.1% of patients after kidney transplant, and the risk was 2.3 times greater in RTRs than in the matched subjects, increasing to 5.4 times in those aged ≥50 years [Kwon JH et al 2015]. Looking at the sub-analysis by gender, even if the results did not reach statistical significance, female gender was a risk factor both at univariate (HR 1.289, 95%CI 0.494-3.365) and at multivariate analysis (HR 1.124, 95% CI 0.380-3.322) [Kwon JH et al 2015]

3. PERSONAL EXPERIENCE USING DATA FROM NATIONAL ITALIAN DATABASE

In 2013, we determined whether an increased WE mortality for acute aortic dissection or rupture (AARD) is present in Italy. Inclusion criteria were: AARD emergency admission with primary ICD-9-CM codes: 441.0—Dissection of aorta, 441.00—Unspecified site, 441.01— Thoracic, 441.02—Abdominal, 441.03—Thoracoabdominal, 441.1—Thoracic aneurysm, ruptured, 441.3—Abdominal aneurysm, ruptured, 441.5—Aortic aneurysm of unspecified site, ruptured, and 441.6—Thoracoabdominal aneurysm, ruptured. The analysis excluded patients with codes 441.2, 441.4, 441.7, 441.9 (no mention of rupture) and 901.0, 902.0 (trauma). Events were analyzed according to day-of-week of admission and occurrence on WE vs. weekdays (WD). Since the database did not provide clinical information, we focused to hard outcomes: fatal (death during hospitalization) and nonfatal (patient discharged alive). Out of 164,321 admissions with the ICD9-CM codes 441-*-Aortic aneurysm and dissection, we first extracted 66,298 emergency admissions. Of these, 17,319 cases, referring to 15,137 patients (mean age 71.1±13 years – yrs), 11,024 males (72.8%, mean age 69.8±12.9 yrs) and 4,113 females (74.5±12.6 yrs, p=0.001) had acute AARD codes (441.00, 441.01, 441.02, 441.03, 441.1, 441.3, 441.5, 441.6). Recurrent hospitalization was recorded in 2182 (12.6%) cases (1,746 different subjects). AARD admissions were most frequent on Monday (16.7%) and less frequent on Saturday (12.1%). A significantly increased mean LOS in WD vs. WE admissions was found for all patients

(13.0±0.17 vs. 12.0±0.26 days, p=0.005) and patients died during hospitalization (8.7±0.38 vs. 6.9±0.49 days, p=0.011), but not for patients discharged alive (14.8±0.18 vs.14.8±0.29 days, p=NS). Mortality was significantly higher in females, aged >80 yrs, subjects admitted on first event, and those admitted on WE. IHM within 24 h from admission was higher among patients admitted on WE vs. WD (52.2% vs. 47.4%, p=0.001). Logistic analysis found an increased in-hospital risk of death (OR [95% C.I.]) related to: admission on WE (1.34 [1.24–1.44], p=0.001), female gender (1.19 [1.11–1.28], p=0.001), increasing age (age <60 yrs as reference, 60–69: 1.60 [1.41–1.82], p< 0.001; 70–79: 2.46 [2.19–2.76], p<0.001; ≥80: 4.67 [4.18–5.24], p<0.001); first event and admission on WE: 1.22 [1.13–1.32], p<0.001. The analysis by anatomical site showed an increased risk of death during WE (OR [95% C.I.]) inpatients with codes 441.0 (1.58 [1.38–1.81], p<0.001), 441.00 (1.71 [1.40–2.10], p<0.001), 441.01 (1.32 [1.10–1.66], p=0.017), 441.03 (1.66 [1.31–2.1], p<0.001), and aortic rupture, all cases (1.28 [1.14–1.43], p<0.001), 441.1 (1.44 [1.08–1.91], p=0.012); 441.3 (1.67 [1.02–1.33], p=0.020); 441.6 (2.06 [1.42–2.99], p<0.001) but not for 441.5 (1.06 [0.59–1.881], p=NS). Interestingly, a significantly lower number of major diagnostic examinations was performed in patients admitted on WE compared to WD. Logistic regression analysis (including WD/WE admission, gender, age subgroups, first or successive admission, diagnostic and therapeutic procedures) confirmed WE admission as independent risk factor for increased mortality (1.34 [1.24–1.44], p=0.001). This study provided further confirmation that AARD patients urgently hospitalized on WE showed highly significant increased risk of death than those admitted on WD. Moreover, they underwent less diagnostic examinations, and WE admission remained an independent risk factor for mortality, regardless of sex, age, site and type of dissection or rupture [Gallerani M et al 2013].

In 2018, we performed a study in order to investigate the mortality rate of patients with acute PE who were hospitalized during WE versus WD. Patients with PE were identified using primary or secondary discharge diagnoses based on the following ICD-9-CM codes: 415.11: iatrogenic PE and infarction, 415.19: another PE and infarction. The day of admission was categorized into seven 1-day intervals for analysis, and the events were classified on the basis of their occurrence on a WE versus a WD. As a proxy of PE severity, any mention of respiratory failure was tracked (ICD-9-CM code 518.8). CCI was applied to identify single diseases (eg, diabetes, chronic obstructive pulmonary disease [COPD], cerebrovascular disease, heart failure, or chronic renal disease) and to derive the overall comorbidity score. Furthermore, the most common infections were identified from discharge codes (some infectious diseases, 001-129; pneumonia and influenza, 580-587; urinary tract infections, 590,595,597,5990).

Overall, 265,035 admissions with a diagnosis of PE were retrieved from January 2001 to December 2014 (mean age: 72.8±14.5 years). Of these, 112,668 events occurred in males (42.5%, mean age: 70.3±14.2 years) and 152,367 in females (57.5%, mean age: 74.7±14.5 years). PE was the primary diagnosis in 198,565 (74.9%) of the analyzed admissions. After exclusion of transfers between hospitals, a small proportion of patients (15,090 of 247,935, 6.1%) had multiple PE events through the 2001 to 2014 period. Hospitalizations with PE increased through study years. IHM was 16.1% overall, decreasing from 21.4% in 2001 to 11.3% in 2014 ($p<0.001$). About the day of admission, 200,166 (75.5%) patients were admitted on WD and 64,869 (24.5%) on WE. Admissions with PE were more frequent on Mondays (41 917 admissions, 15.8% of all events) and less frequent on Saturdays (32,295 admissions, 12.2%) and Sundays (32,574 admissions, 12.3%). IHM was higher among patients admitted during the WE across each study year when analyzed separately, being in the whole period equal to 15.5% on WD and to 17.9% on WE. The prevalence of common comorbidities was higher in patients admitted on WD. IHM was lower among females, increased with age, comorbidity score, and presence of respiratory failure and declined through analyzed years, with a 50% reduction at the end with respect to the beginning of the study period. After adjustment for the above determinants by means of logistic regression, patients admitted on WE were at a significantly increased risk of death during hospitalization. A higher IHM among patients admitted on WE was confirmed also when analyses were restricted to admissions with PE as the primary diagnosis (OR: 1.17, 1.13-1.21), to patients with 1 single PE event through the study period (OR: 1.15, 1.12-1.18), or to the last 4 analyzed years (OR: 1.15, 1.10-1.20), when overall case fatality for PE was lower. Among patients admitted on WE, mortality was increased already on the day of admission and remained higher than among patients hospitalized on WD thorough the first week of hospital stay. We concluded that IHM remained higher among patients admitted during the WE across all years examined, being in the whole study period equal to 15.5% on WD and to 17.9% on WE. Older age, comorbidities (CCI), and WE were independent predictors for IHM [Gallerani M et al 2018].

In 2019, we evaluated the relationship between gender, comorbidity and IHM in patients with acute acute esophageal variceal bleeding (AEVB). AEVB patients were identified using as first or second discharge diagnoses the following ICD-9-CM codes: 456.0 Esophageal varices with bleeding; 456.20 Esophageal varices in diseases classified elsewhere - with bleeding. The modified version of the CCI adapted to ICD-9-CM codes was applied to derive the overall comorbidity score, after excluding mild/severe liver disease (present in all study subjects based on selection criteria). The most common underlying liver diseases were identified from discharge codes: liver cancer (ICD-9-CM 155), alcoholic liver diseases (155.0-155.3), other specified liver diseases (571.4-571.9). The presence of decompensated liver disease was tracked by discharge codes of hepatic encephalopathy (572.2), hepatorenal syndrome (572.4), ascites (789.5), spontaneous bacterial peritonitis (567.2). During the study period 144,943 patients were discharged with a diagnosis of AEVB. Of these, 76,947 (53.1%) were urgent admissions, and only patients with first or second diagnosis of AEVB (n=24,570) were included in the study population, males being 16,724 and females 7,846. About half were aged ≥65 years, and nearly 10% were diagnosed with hepatocellular carcinoma. IHM occurred in 11.8% (2,905 patients; 12.1% males and 11.3% females), with an increasing trend from 9.2% (among subjects aged <55 years) to 18.9% (among the elderly ≥85 years). The raw risk of death was slightly higher among females, but when age and clinical presentation were considered, the female gender was associated to a reduced mortality. The risk of death increased in patients with a diagnosis of hepatocellular carcinoma, alcohol-related liver disease, decompensated liver disease, and, although without a linear relationship, in patients with multiple comorbidities. The mortality rate declined over time. The risk of IHM was reduced in women with non-alcoholic liver disease. Conversely, it was increased in those with alcoholic liver disease, although the relationship did not reach the statistical significance (OR 1.21; 95%IC 0.98-1.50, p= 0.074). To the best of our knowledge, this was the first Italian study evaluating gender differences in AEVB-related IHM derived by a comprehensive analysis of a National database. We found that in the female gender the risk of AEVB-related IHM was lower for non-alcoholic liver disease, but it appeared to be increased in alcoholic liver disease. Recent data indicate an increasing dose-dependent relative risk of developing alcohol-induced liver disease for both men and women. However, women have a significantly higher relative risk of alcohol-related liver disease than men for any level of alcohol intake [Becker U et al 1996]. Hepatic damage could be even worse in postmenopausal women. It has been suggested that a reduced response to estradiol could contribute to a greater progression of hepatic fibrosis and hepatocellular carcinoma in men and postmenopausal women [Shimizu I & Ito S 2007]. Hepatic fibrosis progression due to HBV and HCV infections appears to be slower in females than males [Poynard T et al 2003; Rodríguez-Torres M et al 2006] and menopause is associated with hepatic fibrosis progression, underlying protection of estrogens against progression to chronic liver disease [Shimizu I et al 2007]. The estrogen-mediated mechanisms may be taken into account to explain our results showing a lower risk of AEAB-related IHM in women with non-alcoholic liver disease. In contrast, women appear to be more susceptible to alcohol damage. In fact, compared to men, women have less first-pass alcohol metabolism (due to lower gastric alcohol dehydrogenase activity), show a slower gastric emptying of alcohol and, last but not least, hepatic oxidation is higher in females [Baraona E et al 2001]. These pharmacokinetic features may increase the vulnerability of women to the effects of ethanol. Very recently Italian authors tested the hypothesis of an additive interaction due to simultaneous presence of HBV, HCV and alcohol intake on the risk of development of cirrhosis. They found an additive interaction in females, but not in males [Stroffolini T et al 2017]. AEVB-related IHM is decreasing and in most cases, involves aged comorbid patients with different liver diseases. Although men remain at high risk, female gender appears to be protective only in those with non-alcoholic liver disease, whereas the risk increases in females with alcoholic liver disease. Overall the risk of AEVB and related IHM is increased in any patients with multiple comorbidities [Fabbian F et al 2019].

VI. CONCLUSIONS

Administrative databases derive from claims made for services by health care providers. The reasons for their development were therefore different from reasons related to epidemiologic research. Commonly they include basic demographic information and those related to hospitalizations, outpatients visits and drug dispensing. These data are collected for management purpose, not for research. Some statistical associations detected by their analysis could be misleading and patients enrolled could not be representative of the population of interest. Some conditions known to be risk factors for mortality, such as hypertension and diabetes, are under-reported and paradoxically could appear to be protective. The latter effect is due to codification bias, i.e. they were codified only in "fit" patients. Also, temporal sequences of events are not defined, we do not know if a condition is acquired in community or during hospitalization.

Careful evaluation of comorbidity is important in internal medicine ward patients hospitalized for infectious disease, being in-hospital mortality related to severity of disease, and to multimorbidity. In these patients, a careful evaluation of comorbidity should represent a fundamental step in the disease management. Regional administrative database showed that costs related to admissions of a specific population such as renal transplant recipients gradually increased probably due to the increasing number of admissions and increasing age. Using these large databases, it is possible to evaluate large number of patients and different hospital settings. Administrative databases contain information on demographic, type of hospital where care take place, diagnosis, procedures, length of stay and discharge status. Researchers could select specific conditions and procedures knowing hard outcomes such as mortality. Although administrative databases underestimate some diseases, it has been shown that they are reliable regarding comorbidity. Comorbidity needs to be taken into account in order to reduce potential confounding in epidemiological research and administrative databases allow the development of new comorbidity indexes. Then in the first part of the work it was reported that comorbidity was a risk factor for in-hospital mortality in subjects admitted with infectious diseases. Indirectly, we also tested a new comorbidity score. Finally, we used the regional administrative database for testing a function peculiar for these files. We evaluated costs of renal transplant hospitalizations.

We conclude that administrative databases are extremely important for health care professionals; they allow to investigate associations and to develop comorbidity indexes that could be used for clinical management research.

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VIII. APPENDICES

APPENDIX I: TABLE A: PUBLICATIONS; TABLE B: CONFERENCE PRESENTATIONS

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (1/6)

	Authors	**Title**	**Journal, year**	**Rank Quartile (Q) ISI Branch**	**Impact factor ISI 2018**
1	Manfredini R, Cappadona R, **Fabbian F.**	Heat Stress and Cardiovascular Mortality in Immigrant Workers: Can We Do Something More?	Cardiology. 2019 Jul 16:1-3. doi: 10.1159/000501261.	103/136 Q4 Cardiac & Cardiovascular systems	1.561
2	Di Simone E, Di Muzio M, Dionisi S, Giannetta N, Di Muzio F, De Gennaro L, Orsi GB, **Fabbian F.**	Infodemiological patterns in searching medication errors: relationship with risk management and shift work.	Eur Rev Med Pharmacol Sci. 2019;23(12):5522-5529.	123/267 Q2 Pharmacology & Pharmacy	2.721
3	Di Muzio M, Dionisi S, Di Simone E, Cianfrocca C, Di Muzio F, **Fabbian F,** Barbiero G, Tartaglini D, Giannetta N.	Can nurses' shift work jeopardize the patient safety? A systematic review.	Eur Rev Med Pharmacol Sci. 2019;23(10):4507-4519.	123/267 Q2 Pharmacology & Pharmacy	2.721
4	Balla C, Malagu' M, **Fabbian F,** Guarino M, Zaraket F, Brieda A, Smarrazzo V, Ferrari R, Bertini M.	Prognosis after pacemaker implantation in extreme elderly.	Eur J Intern Med. 2019;65:37-43.	27/160 Q1 Medicine, General & Internal	3.660
5	López-Soto PJ, Morales-Cané I, **Fabbian F**, Manfredini R, Dios-Guerra C, Carmona-Torres JM, Rodríguez-Borrego MA.	Characteristics of the Spanish Older People in the Use of Accidents and Emergency Unit Services (2014-2017).	Clin Nurs Res. 2019 Apr 21. doi: 10.1177/1054773819843627.	42/120 Q2 Nursing	1.500

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (2/6)

	Authors	**Title**	**Journal, year**	**Rank Quartile (Q) ISI Branch**	**Impact factor ISI 2018**
6	Manfredini R, **Fabbian F,** De Giorgi A, Cappadona R, Capodaglio G, Fedeli U.	Daylight saving time transitions and circulatory deaths: data from the Veneto region of Italy.	Intern Emerg Med. 2019 Apr 9. doi: 10.1007/s11739-019-02085-5.	52/160 Q2 Medicine, General & Internal	2.335
7	Manfredini R, **Fabbian F,** Cappadona R, De Giorgi A, Bravi F, Carradori T, Flacco ME, Manzoli L.	Daylight Saving Time and Acute Myocardial Infarction: A Meta-Analysis.	J Clin Med. 2019;8(3). pii: E404.	15/160 D1 Q1 Medicine, General & Internal	5.688
8	**Fabbian F,** Tonelli L, De Giorgi A, Cappadona R, Pasin M, Manfredini R.	Early prognostic value of nocturnal blood pressure: a single-centre experience.	Blood Press Monit. 2019;24(3):120-122.	62/65 Q4 Peripheral Vascular Disease	1.008
9	Manfredini R, Cappadona R, **Fabbian F.**	Is Takotsubo Syndrome Still a Benign Disease? Complications (and Gender) Make the Difference.	Angiology. 2019 Feb 14. doi: 10.1177/0003319719830011.	35/65 Q3 Peripheral Vascular Disease	2.376
10	**Fabbian F**, Fedeli U, De Giorgi A, Cappadona R, Guarino M, Gallerani M, De Giorgio R, Manfredini R.	Sex and acute oesophageal variceal bleeding-related in-hospital mortality: a 15-year retrospective study.	Eur Rev Med Pharmacol Sci. 2019;23(2):811-817.	123/267 Q2 Pharmacology & Pharmacy	2.721
11	Manfredini R, Cappadona R, De Giorgi A, **Fabbian F.**	To Marry or Not.	Am J Cardiol. 2019;123(7):1185	59/136 Q2 Cardiac & Cardiovascular Systems	2.843

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (3/6)

	Authors	**Title**	**Journal, year**	**Rank Quartile (Q) ISI Branch**	**Impact factor ISI 2018**
12	**Fabbian F**, Verzola A, Napoli N, De Giorgi A, Comai G, La Manna G, Gallerani M, Manfredini R, Rodríguez-Borrego MA, López-Soto PJ.	Impact of hospital admissions subsequent to renal transplantation on Italian regional resources: a retrospective study in the region Emilia-Romagna.	Minerva Urol Nefrol. 2019 Jan 17. doi: 10.23736/S0393-2249.19.03280-6.	29/80 Q2 Urology & Nephrology	2.477
13	Manfredini R, Cappadona R, **Fabbian F.**	Nurses, shift work, and diabetes: should late chronotype be considered as a risk factor?	BMJ. 2019;364:l178.	5/160 D1 Q1 Medicine, General & Internal	27.604
14	López-Soto PJ, **Fabbian F**, Cappadona R, Zucchi B, Manfredini F, García-Arcos A, Carmona-Torres JM, Manfredini R, Rodríguez-Borrego MA.	Chronotype, nursing activity, and gender: A systematic review.	J Adv Nurs. 2019;75(4):734-748.	13/120 Q1 Nursing	2.376
15	Manfredini R, **Fabbian F**, Cappadona R, De Giorgio R, Grassi L.	A time of day for aggressive behavior? Possible insights for ED personnel.	Am J Emerg Med. 2019;37(1):153-155.	14/29 Q2 Emergency Medicine	1.651
16	Manfredini R, Lamberti N, Manfredini F, Straudi S, **Fabbian F**, Rodriguez Borrego MA, Basaglia N, Carmona Torres JM, Lopez Soto PJ.	Gender Differences in Outcomes Following a Pain-Free, Home-Based Exercise Program for Claudication.	J Womens Health (Larchmt). 2018 Sep 15. doi: 10.1089/jwh.2018.7113.	6/44 Q1 Womens studies	2.009

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (4/6)

	Authors	Title	Journal, year	Rank Quartile (Q) ISI Branch	Impact factor ISI 2018
17	**Fabbian F**, De Giorgi A, Cappadona R, Gozzi D, Pasin M, De Giorgio R, Manfredini R.	Hypertension, abnormal blood pressure circadian pattern, and frailty: data from the literature.	J Geriatr Cardiol. 2018;15(12):747-750.	95/136 Q3 Cardiac & Cardiovascular Systems	1.763
18	**Fabbian F**, De Giorgi A, Boari B, Misurati E, Gallerani M, Cappadona R,Cultrera R, Manfredini R, Rodrìguez Borrego MA, Lopez-Soto PJ.	Infections and internal medicine patients: Could a comorbidity score predict in-hospital mortality?	Medicine (Baltimore). 2018;97(42):e12818.	69/160 Q2 Medicine, General & Internal	1.870
19	Manfredini R, **Fabbian F**, De Giorgi A, Cappadona R, Zucchi B, Storari A, Rodriguez Borrego MA, Carmona Torres JM, Lopez Soto PJ.	Takotsubo syndrome and dialysis: an uncommon association?	J Int Med Res. 2018;46(11):4399-4406.	112/136 Q4 Medicine, Research & Experimental	1.351
20	Manfredini R, **Fabbian F,** Cappadona R, Modesti PA.	Daylight saving time, circadian rhythms, and cardiovascular health.	Intern Emerg Med. 2018;13(5):641-646.	52/160 Q2 Medicine, General & Internal	2.335
21	Manfredini R, De Giorgio R, **Fabbian F**.	Off-Hours and In-Hospital Mortality: Lower Resources or Higher Severity?	J Am Coll Cardiol. 2018;71(21):2492.	3/136 D1 Q1 Cardiac & Cardiovascular Systems	18.639

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (5/6)

	Authors	Title	Journal, year	Rank Quartile (Q) ISI Branch	Impact factor ISI 2018
22	**Fabbian F**, De Giorgi A, Tiseo R, Cappadona R, Zucchi B, Rubbini M, Signani F, Storari A, De Giorgio R, La Manna G, Manfredini R.	Neoplasms and renal transplantation: impact of gender, comorbidity and age on in-hospital mortality. A retrospective study in the region Emilia-Romagna of Italy.	Eur Rev Med Pharmacol Sci. 2018;22(8):2266-2272.	123/267 Q2 Pharmacology & Pharmacy	2.721
23	Rubbini M, Ascanelli S, **Fabbian F**.	Hemorrhoidal disease: is it time for a new classification?	Int J Colorectal Dis. 2018;33(6):831-833.	59/203 Q2 Surgery	2.641
24	Manfredini R, **Fabbian F**, Cappadona R, Zucchi B, Lopez-Soto PJ, Rodriguez-Borrego MA.	Attempted suicide as a trigger of Takotsubo syndrome: a minireview of available case reports.	Intern Emerg Med. 2018;13(4):629-631.	52/160 Q2 Medicine, General & Internal	2.335
25	Manfredini R, **Fabbian F**, De Giorgi A, Zucchi B, Cappadona R, Signani F, Katsiki N, Mikhailidis DP.	Daylight saving time and myocardial infarction: should we be worried? A review of the evidence.	Eur Rev Med Pharmacol Sci. 2018;22(3):750-755.	123/267 Q2 Pharmacology & Pharmacy	2.721
26	Manfredini R, **Fabbian F.**	Pulmonary embolism, mortality, 'weekend effect' and gender: what do we know?	Future Cardiol. 2018;14(1):9-13.	Not provided	Not provided

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (6/6)

	Authors	**Title**	**Journal, year**	**Rank Quartile (Q) ISI Branch**	**Impact factor ISI 2018**
27	Gallerani M, Fedeli U, Pala M, De Giorgi A, **Fabbian F**, Manfredini R.	Weekend Versus Weekday Admission and In-Hospital Mortality for Pulmonary Embolism: A 14-Year Retrospective Study on the National Hospital Database of Italy.	Angiology. 2018;69(3):236-241.	35/65 Q3 Peripheral Vascular Disease	2.376
28	López-Soto PJ, García-Arcos A, **Fabbian F**, Manfredini R, Rodríguez-Borrego MA.	Falls Suffered by Elderly People From the Perspective of Health Care Personnel: A Qualitative Study.	Clin Nurs Res. 2018;27(6):675-691.	42/120 Q2 Nursing	1.500

Paper published by research group in which the doctoral student was involved as an investigator in 2018 and 2019

1. Carlotta F, Raffaella R, Ilaria A, Alessandro N, Mannuccio MP; REPOSI Collaborators. Prevalence of use and appropriateness of antidepressants prescription in acutely hospitalized elderly patients. Eur J Intern Med. 2019 Aug
9. pii: S0953-6205(19)30258-4. doi: 10.1016/j.ejim.2019.07.025.
2. Paciullo F, Proietti M, Bianconi V, Nobili A, Pirro M, Mannucci PM, Lip GYH, Lupattelli G; REPOSI Investigators. Choice and Outcomes of Rate Control versus Rhythm Control in Elderly Patients with Atrial Fibrillation: A Report from the REPOSI Study. Drugs Aging. 2018;35(4):365-373.
3. Raparelli V, Pastori D, Pignataro SF, Vestri AR, Pignatelli P, Cangemi R, Proietti M, Davì G, Hiatt WR, Lip GYH, Corazza GR, Perticone F, Violi F, Basili S; ARAPACIS Study Collaborators. Major adverse cardiovascular events in non-valvular atrial fibrillation with chronic obstructive pulmonary disease: the ARAPACIS study. Intern Emerg Med. 2018;13(5):651-660.
4. Bossone E, Arcopinto M, Iacoviello M, Triggiani V, Cacciatore F, Maiello C, Limongelli G, Masarone D, Perticone F, Sciacqua A, Perrone-Filardi P, Mancini A, Volterrani M, Vriz O, Castello R, Passantino A, Campo M, Modesti PA, De Giorgi A, Monte I, Puzzo A, Ballotta A, Caliendo L, D'Assante R, Marra AM, Salzano A, Suzuki T, Cittadini A; TOSCA Investigators. Multiple hormonal and metabolic deficiency syndrome in chronic heart failure: rationale, design, and demographic characteristics of the T.O.S.CA. Registry. Intern Emerg Med. 2018;13(5):661-671.
5. Proietti M, Antoniazzi S, Monzani V, Santalucia P, Franchi C; SIM-AF Investigators, Fenoglio LM, Melchio R, Fabris F, Sartori MT, Manfredini R, De Giorgi A, **Fabbian F**, Biolo G, Zanetti M, Altamura N, Sabbà C, Suppressa P, Bandiera F, Usai C, Murialdo G, Fezza F, Marra A, Castelli F, Cattaneo F, Beccati V, di Minno G, Tufano A, Contaldi P, Lupattelli G, Bianconi V, Cappellini D, Hu C, Minonzio F, Fargion S, Burdick L, Francione P, Peyvandi F, Rossio R, Colombo G, Monzani V, Ceriani G, Lucchi T, Brignolo B, Manfellotto D, Caridi I,

Corazza GR, Miceli E, Padula D, Fraternale G, Guasti L, Squizzato A, Maresca A, Liberato NL, Tognin T, Rozzini R, Bellucci FB, Muscaritoli M, Molfino A, Petrillo E, Dore M, Mete F, Gino M, Franceschi F, Gabrielli M, Perticone F, Perticone M, Bertolotti M, Mussi C, Borghi C, Strocchi E, Durazzo M, Fornengo P, Dallegri F, Ottonello LC, Salam K, Caserza L, Barbagallo M, Di Bella G, Annoni G, Bruni AA, Odetti P, Nencioni A, Monacelli F, Napolitano A, Brucato A, Valenti A, Castellino P, Zanoli L, Mazzeo M. Use of oral anticoagulant drugs in older patients with atrial fibrillation in internal medicine wards. Eur J Intern Med. 2018;52:e12-e14.

6. Franchi C, Antoniazzi S, Proietti M, Nobili A, Mannucci PM; SIM-AF Collaborators. Appropriateness of oral anticoagulant therapy prescription and its associated factors in hospitalized older people with atrial fibrillation. Br J Clin Pharmacol. 2018;84(9):2010-2019.

7. Raparelli V, Pastori D, Pignataro SF, Vestri AR, Pignatelli P, Cangemi R, Proietti M, Davì G, Hiatt WR, Lip GYH, Corazza GR, Perticone F, Violi F, Basili S; ARAPACIS Study Collaborators. Correction to: Major adverse cardiovascular events in non-valvular atrial fibrillation with chronic obstructive pulmonary disease: the ARAPACIS study. Intern Emerg Med. 2018;13(8):1349.

8: Mannucci PM, Nobili A, Pasina L; REPOSI Collaborators (REPOSI is the acronym of REgistro POliterapie SIMI, Società Italiana di Medicina Interna). Polypharmacy in older people: lessons from 10 years of experience with the REPOSI register. Intern Emerg Med. 2018;13(8):1191-1200.

9: Proietti M, Agosti P, Lonati C, Corrao S, Perticone F, Mannucci PM, Nobili A, Harari S; REPOSI Investigators. Hospital Care of Older Patients With COPD: Adherence to International Guidelines for Use of Inhaled Bronchodilators and Corticosteroids. J Am Med Dir Assoc. 2019 Mar 6. pii: S1525-8610(19)30159-8. doi: 10.1016/j.jamda.2019.01.132.

Table B. Conference presentations that the doctoral student has carried out in the period 2018-2019

	Authors	Conference, City, Date	Type	Title
1	**Fabbian Fabio**, De Giorgi Alfredo, Gozzi Dario, Pasin Mauro, Storari Alda, Gallerani Massimo, Manfredini Roberto	59° Congresso Nazionale della Società Italiana di Nefrologia. Rimini 3-6 Ottobre 2018	Oral presentation	Risk factors for inhospital mortality in elderly patients admitted because of acute renal failure: a nationwide retrospective study
2	Fabbian Fabio	24th World Cardiology Conference, Hong Kong, September 17-18, 2018	Oral presentation	Abnormal blood pressure circadian pattern and multimorbidity: what does come first?
3	Fabbian Fabio	Insontro clinic-scientifici, Sciola di Specializzazione endocrinologia e Mamattie del metabolismo, Ferrara, 23 marzo 2019	Oral presentation	Metformina: vecchie e nuove potenzialità, malattie renali
4	De Giorgi A, **Fabbian F**, Guarino M, Bagnaresi I, Salmi R, Gallerani M, De Giorgio R, Manfredini R.	119° Congresso Nazionale della Società Italiana di Medicina Interna, Roma 26-28 Ottobre 2018	Poster	In-hospital mortality in elderly patients admitted for acute renal failure: does a weekend effect exist? a nationwide retrospective study.
5	Guarino M, De Giorgi A, **Fabbian F**, Spampinato MD, Gallerani M, Salmi R, De Giorgio R, Manfredini R.	119° Congresso Nazionale della Società Italiana di Medicina Interna, Roma 26-28 Ottobre 2018	Poster	Acute esophageal variceal bleeding and in-hospital mortality: does gender matter? A retrospective study in Italy.
6	De Giorgi A, Bonazzi S, **Fabbian F**, Guarino M, Leonardo A, Salmi R, De	119° Congresso Nazionale della Società Italiana di	Poster	Spindle cell tumor of the liver: an uncommon case of an uncommon tumor in elderly.

	Giorgio R, Manfredini R.	Medicina Interna, Roma 26-28 Ottobre 2018		
7	De Giorgi A, **Fabbian F**, Pasin M, Tonelli L, Guarino M, Bagnaresi I, De Giorgio R, Manfredini R.	119° Congresso Nazionale della Società Italiana di Medicina Interna, Roma 26-28 Ottobre 2018	Poster	Ambulatory blood pressure monitoring during pregnancy: a single center italian experience.

APPENDIX II: CHARLSON COMORBIDITY INDEX (CHARLSON ME ET AL. 1987)

Points assigned to different conditions in order to calculate the Charlson comorbidity score

Conditions	Weights
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular Disease	1
Cerebrovascular Disease	1
Chronic Obstructive Pulmonary Disease	1
Dementia	2
Paraplegia and Hemiplegia	1
Diabetes	1
Diabetes with Complications	2
Renal Disease	2
Mild Liver Disease	1
Moderate or Severe Liver Disease	3
Peptic Ulcers	1
Rheumatic Disease	1
Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS)	6
Cancer	2
Metastatic Solid Tumor	6

APPENDIX III: ELIXHAUSER COMORBIDITY INDEX (ELIXHAUSER A ET AL. 1998)

Points assigned to different conditions in order to calculate the Elixhauser Index

Conditions	**Score (due to addition of diagnosed conditions)**
1. Congestive Heart Failure	Yes=1/No=0
2. Cardiac Arrhythmia	Yes=1/No=0
3. Valvular Disease	Yes=1/No=0
4. Pulmonary Circulation Disorders	Yes=1/No=0
5. Peripheral Vascular Disorders	Yes=1/No=0
6a. Hypertension Uncomplicated	Yes=1/No=0
6b. Hypertension Complicated	Yes=1/No=0
7. Paralysis	Yes=1/No=0
8. Other Neurological Disorders	Yes=1/No=0
9. Chronic Pulmonary Disease	Yes=1/No=0
10. Diabetes Uncomplicated	Yes=1/No=0
11. Diabetes Complicated	Yes=1/No=0
12. Hypothyroidism	Yes=1/No=0
13. Renal Failure	Yes=1/No=0
14. Liver Disease	Yes=1/No=0
15. Peptic Ulcer Disease excluding bleeding	Yes=1/No=0
16. AIDS/HIV	Yes=1/No=0
17. Lymphoma	Yes=1/No=0
18. Metastatic Cancer	Yes=1/No=0
19. Solid Tumor without Metastasis	Yes=1/No=0
20. Rheumatoid Arthritis/collagen	Yes=1/No=0
21. Coagulopathy	Yes=1/No=0
22. Obesity	Yes=1/No=0
23. Weight Loss	Yes=1/No=0
24. Fluid and Electrolyte Disorders	Yes=1/No=0
25. Blood Loss Anemia	Yes=1/No=0
26. Deficiency Anemia	Yes=1/No=0
27. Alcohol Abuse	Yes=1/No=0
28. Drug Abuse	Yes=1/No=0
29. Psychoses	Yes=1/No=0
30. Depression	Yes=1/No=0

APPENDIX IV: MODIFIED ELIXHAUSER SCORE (FABBIAN F ET AL. 2017)

Points assigned to different conditions in order to calculate the modified Elixhauser' index.

Conditions	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
Chronic kidney disease	1
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