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Cluster-based epidemiological assessment in patients admitted to internal medicine with at least one of the following diagnoses: heart failure, chronic obstructive pulmonary disease or renal failure. The InCLuDimi study

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Patient consent for publication: patient consent for publication was obtained. All data were anonymized to ensure confidentiality, and no identifying information is included in this manuscript.

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Introduction

Advances in medical care have increased both the age and clinical complexity of patients admitted to internal medicine wards, with multiple chronic conditions significantly impacting outcomes and treatment. Multimorbidity, common in older adults, rises with age: Medicare data indicate that 32% of individuals aged 65-69 years have three or more chronic conditions, exceeding 50% in those aged 80-84 years.[1] It is associated with higher mortality, disability, functional decline, and poorer quality of life. Multimorbidity challenges treatment appropriateness, as most clinical practice guidelines are disease-oriented, and this concept could be reductive, not implying shared pathophysiology.[2] Similarly, comorbidity—additional conditions subordinate to an index disease—fails to capture internal medicine complexity.[2,3] Schäfer *et al.* likened multimorbidity to a maze of statistical disease associations, advocating separation of random from significant comorbidity, identification of disease clusters, and analysis of age- and sex-specific patterns.[4] Subsequent studies emphasize clusters: nosographic groupings of statistically associated conditions with an index disease, revealing congruences, interconnections, and interactions. Clusters may share genetic, individual, or environmental factors, aiding prevention and management. Schäfer *et al.* identified three clusters (cardiovascular/metabolic, neuropsychiatric, anxiety/depression) covering ~50% of those >65 years, urging research on inter-cluster interactions and synergistic effects.[4] Other studies show heterogeneous results due to varying designs, data sources (*e.g.*, administrative registries, surveys), populations (*e.g.*, US veterans, American Indians), and diagnoses, yet patterns overlap and influence each other.[4-7] Therapeutically, clusters minimize polypharmacy harm by balancing chronic conditions, life expectancy, care goals, and preferences against medication benefits/risks, guiding decisions on discontinuation, drug interactions, and guideline deviations.[4,8,9] Heart failure, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD)—top hospitalization causes—form clusters with distinct geographical/socio-economic distributions and shared mechanisms.[8-10] The FADOI Young Investigators Group plans an Italian observational study to identify clusters linked to these, exploring interconnections, interactions, and risk factors. These chronic conditions will be defined according to standardised criteria using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.[11] The primary objective of the study is to identify and assess the prevalence of the most frequent disease clusters in the Internal Medicine setting among groups of patients with at least one of the following chronic conditions: heart failure (with preserved or reduced left ventricular systolic function), COPD and CKD. The predefined secondary objectives are to assess the association between the different clusters and adverse clinical outcomes (during hospitalisation and at 30 days after discharge), to identify potential risk factors associated with the development of clusters, and to assess the prevalence of clusters in defined patient subgroups.

Endpoints

Primary endpoint

- Identification of disease clusters.

Disease clusters will be defined as the concomitant presence of at least two additional chronic conditions (according to the definition of disease clusters used in the REPOSI study) in patients with at least one of the following chronic conditions:[12]

- Heart failure
- COPD
- CKD

Secondary endpoints

- To identify potential risk factors associated with the development of disease clusters.
- To assess the prevalence of clusters in patient subgroups (age categories, sex, geographical distribution).
- To identify the cluster associated with the highest in-hospital mortality.

- To identify the cluster associated with the highest 30-day post-discharge mortality.
- To identify the cluster associated with the highest 30-day hospital readmission rate.

Study design and patient characteristics

Study design

This is a national, multicenter, prospective, observational study involving approximately 50 Internal Medicine Units, each expected to consecutively enrol about 100 adult inpatients with at least one of the following chronic conditions: heart failure, COPD or CKD**,** admitted to Internal Medicine wards, for a minimum of 1500 subjects per disease group. The study is a non-profit scientific project promoted by the FADOI ("Federation of Associations of Hospital Internists Directors") Foundation, established by the homonymous Scientific Society FADOI.

Patient selection criteria

Inclusion criteria

- Adult patients admitted to Internal Medicine wards with a diagnosis of at least one of the following chronic conditions: heart failure, COPD and/or CKD.

Specifically, the following patients will be enrolled:

- Heart failure defined as a clinical syndrome characterised by typical symptoms (*e.g.*, dyspnoea, peripheral oedema and fatigue) that may be accompanied by signs (*e.g.*, elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, with elevated brain natriuretic peptide levels, in accordance with the 2016 European Society of Cardiology Guidelines.[13] In this study, patients with heart failure with preserved left ventricular ejection fraction (LVEF>50%), mildly reduced LVEF (LVEF 40-50%) or reduced LVEF (LVEF<40%) will be included.
- COPD defined by spirometric demonstration of irreversible airflow obstruction of any severity.[14] In the absence of spirometric data, patients with documented at least one exacerbation requiring hospitalisation may be included.
- CKD is defined as the presence of structural or functional kidney abnormalities for more than 3 months, with implications for health, classified according to cause, eGFR category and albuminuria category. Patients in stages IIIa, IIIb, IV and V will be included; eGFR will be estimated using the Modification of Diet in Renal Disease equation in accordance with the 2012 Kidney Disease Improving Global Outcomes guidelines.[15]
- Written informed consent to participate in the study.

Exclusion criteria

- Patients who do not provide consent to participate in the study.

Data collection

Data protection

To protect patient privacy, data will be entered into a secure electronic database with restricted and controlled access, using a numerical code identifying the study center and a progressive individual number for each patient. Neither patient initials nor date of birth nor other identifiable personal data will be recorded. The study will use a computerized case report form developed by the Promoters and the Scientific Board. The form is designed to minimize the workload for the investigator and to make anonymized data immediately available to the Promoter, thus allowing both a priori quality control of data entry (through logical checks to prevent incongruent data) and remote verification of the collected data. Access to the electronic case report form will be password-protected. Each investigator authorized by the competent Ethics Committee will be assigned a personal password enabling access to the data of their own center only, with the possibility to read and, if necessary, modify records, with full traceability of user identity and timestamps for each entry or modification. Patient data will be stored in the database in anonymized form, and only the investigators will be

able to link the code to the identity of the subject. Completion of the electronic case report form will be based on official clinical documents, particularly hospital medical records. In cases where follow-up information is obtained by telephone contact, the study-specific electronic case report form will be considered as the source document.

Patient enrolment

Enrolment at each center will commence after obtaining all required local approvals.
At the time of enrolment, the following information will be collected:

- Demographic variables
- Age, sex, ethnicity, smoking status.
  - Medical history variables
    - Setting of origin (home, nursing home/long-term care facility).
    - Hospital admissions in the previous year/month.
    - Functional autonomy in basic activities of daily living and instrumental activities of daily living.
    - Barthel Index score, where available.
  - Past medical history
- Heart failure (specifying, where available, NYHA class), COPD, CKD (specifying, where available, severity stage), arterial hypertension, asthma, diabetes mellitus (specifying whether uncomplicated, *i.e.*, without organ damage, or with established organ damage), chronic anemia (hemoglobin <13.0 g/dL in men, <12 g/dL in women), dyslipidemia, active solid malignancy (on curative or palliative systemic and/or radiotherapy), active hematological malignancy (on curative or palliative systemic and/or radiotherapy), ischemic heart disease, atrial fibrillation, cerebrovascular disease (transitory ischemic attack/stroke), Parkinson's disease/other neurodegenerative diseases, thyroid disease (hyperthyroidism, hypothyroidism), liver cirrhosis, dementia/cognitive impairment, autoimmune diseases, chronic inflammatory bowel disease, anxiety disorders, depressive disorders, peripheral arterial occlusive disease of the lower limbs, rheumatologic diseases, AIDS, peptic ulcer disease.
- Reason for admission defined as the clinical problem that led to hospitalization, including specifically:
  - Acute infectious disease
  - Acute heart failure
  - Exacerbation of COPD
  - Pulmonary embolism
  - Acute bleeding
  - Acute kidney injury (regardless of underlying cause)
  - Ischaemic/haemorrhagic stroke
  - Acute coronary syndrome
  - Acute pancreatitis
  - Polytrauma
  - Cirrhosis/chronic liver disease
  - Drug-induced iatrogenic injury
  - Acute glycaemic decompensation
  - Electrolyte or metabolic disorders
  - Social problems (difficult home management)
  - Other.
- Medications/Treatments
- Number of drugs taken at home (before admission) and at discharge.
- Drug classes taken at home and at discharge.
- Scores

- Charlson Comorbidity Index.
- In-hospital outcome
- Discharge (home/nursing home or long-term care facility), death, transfer to intensive care.
- 30-day telephone follow-up
- Mortality and rehospitalization within 30 days after discharge.

Sample size and statistical analysis

Assuming that a clinically relevant prevalence of disease clusters is 25% and accepting a precision of ±2.5% around this estimate (95% confidence interval), a sample of 1252 patients per chronic condition is required. An algorithm based on Partitioning Around Medoids will be used to assign patients to different clinical clusters according to the coexisting conditions listed above. Clusters with a prevalence below 10% of the population will not be considered, as they are deemed to be of limited clinical relevance.

Data will be summarised using standard descriptive statistics. Categorical variables will be reported as counts and percentages. Continuous variables will be expressed as mean and standard deviation or median and interquartile range, according to their distribution.

For each selected chronic condition (COPD, heart failure, CKD), the prevalence of the most frequent clusters will be estimated together with their 95% confidence intervals (calculated using continuity correction where appropriate). Potential risk factors for the most prevalent cluster will first be evaluated by univariate analysis. Subsequently, the independent role of variables that are significant or borderline significant ($p<0.10$) in univariate analyses will be assessed using multivariable binary logistic regression, including the recruiting center as an additional dummy variable. Results of multivariable analyses will be reported as odds ratios with corresponding 95% confidence intervals.

The independent effect of the various risk factors on time-to-event outcomes will be assessed using Cox proportional hazards regression. Variables significant (or borderline significant) in univariate time-to-event analyses will be entered into the model, while the different clusters will be forced into the multivariable model regardless of their univariate association. Results will be reported as hazard ratios with 95% confidence intervals. Statistical analyses will be carried out using STATA (version 2021) and SPSS (version 19).

Ethical and regulatory aspects

The study will be conducted in accordance with the Declaration of Helsinki (Fortaleza 2013 version) and in compliance with current regulations on clinical studies and good clinical practice. The protocol will be submitted to the Coordinating Center Ethics Committee for evaluation and issuance of a Single Opinion, and notified to the Ethics Committees responsible for the other Centers participating in the study. In accordance with Regulation (EU) 2016/679 and Italian Legislative Decree 101/2018, all patients will be required to sign a written informed consent form, with particular reference to the processing of personal data.

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