PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study.
AUTHORS	Baré, Marisa; Herranz, Susana; Roso-Llorach, Albert; Jordana, Rosa; Violán, Concepción; Lleal, Marina; Roura-Poch, Pere; Arellano, Marta; Estrada, Rafael; Nazco, Gloria Julia

VERSION 1 – REVIEW

REVIEWER	Mino-León, Dolores Instituto Mexicano del Seguro Social, Unidad de Investigación Médica en Epidemiología Clínica
REVIEW RETURNED	16-Mar-2021

GENERAL COMMENTS	The paper is interesting and provides information, despite being a difficult subject to approach. However, some changes need to be made to avoid confusion. - Page 5, paragraph 2, line 95-98, it is necessary to be more specific. - I suggest included in the background a paragraph related to the soft clustering method. - Page 8, paragraph 2, lines 157-161; I suggest to explain in depth the coding of clinical management and connect it with the data that present on page 10, paragraph 2, lines 200-204. - Review the use of the abbreviation (R) throughout the document (for example page 10, paragraph 2, lines 201, 207 y 215). - Page 10, lines 205-207; a deep explanation of this paragraph is necessary, it is not enought for understand the main idea. - Page 11, paragraph 2, lines 227-228, review if is characterize diseases or individuals. - Page 11, paragraph 3, line 233: Instead "a disease" "chronic conditions (CC)" and instead of “syndrome”, geriatric syndrome (GS). - Table 1. The variable score of clinical management was missing. - Page 14, paragraph 2, line 274-275, Check the title of table 4 of the supplement, the information is inconsistent. - It seems to me that the text on page 17, paragraph 4, lines 343-345 should be the main focus of the discussion.

REVIEWER	Polidori, M Universitat zu Koln
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	The work presented is related to a certainly highly important topic, i.e. that of multimorbidity clustering with advancing age and its profiling as far as presence of geriatric syndromes is concerned.

	While a very careful analysis of the observations yields a good deal of potentially relevant, clinically useful data for better management of older inpatients, the authors appear to have missed the very core of their results - so that the paper in its present form seems largely confirmatory, quite aspecific and not really vehicle of practical implication for the readers. Several premises, instruments, endpoints and conclusions indicate lack of familiarity with the topic of aging medicine and unfortunately deeply twist the whole picture. First of all, the focus of the work since its design is tightly kept on multimorbidity and chronological age, which completely obfuscates the true patient-centered approach (term used by the authors but unfortunately not applied in their study): multidimensional, comprehensive evaluation beyond organ disease, evaluation and management of the impairment of intrinsic capacity and close value-based assessment of quality of life. Accordingly, the authors chose to scale patients' chronic conditions based on the level of clinical management required both at admission and during hospitalization instead than based on the impact on patients' quality of life. This way, the authors shifted the attention from the patient to the management needed, thereby missing critical information for the purpose of their study. For example, Cluster 3 will typically cause less management effort but negatively impact on quality of life and very often induce the onset or worsening of several geriatric syndroms including isolation, cognitive decline and instability. As a (an important) corollary, it is very difficult to understand that the CM score was given on a subjective, i.e. not validated basis and that no standardized method of assessment was used to diagnose geriatric syndromes. Additionally, not only frailty was categorised as a geriatric syndrom in spite of recent developments, but this very central feature of older inpatients was diagnosed with highly dishomogeneous methods very poorly capturing complexity of frailty and therefore its presence and severity degree. One relevant limitation is that the fundamental source of critical information for the medical community, i.e. Table 4, fully escapes discussion. Important information on the number and nature of geriatric syndromes present in each cluster might offer to healthcare practitioners a path to access a great number of factors strongly influencing patients' trajectories but systematically escaping diagnostic algorithms and codes in real life. The style should be adjusted and some generic expressions (like "makes sense") might be avoided.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Dolores Mino-León, Instituto Nacional de Geriatría, Ministerio de Salud

Comments to the Author:

The paper is interesting and provides information, despite being a difficult subject to approach. However, some changes need to be made to avoid confusion.

We thank the reviewer for the insightful and detailed comments on the whole manuscript. We have addressed all the comments individually:

- Page 5, paragraph 2, line 95-98, it is necessary to be more specific.

We have changed the sentence specifying that the approaches in multimorbidity analyses which are still in question refer to which conditions to consider and how to aggregate them (lines 96-97).

- I suggest included in the background a paragraph related to the soft clustering method.

Thank you for your suggestion. We have added new paragraph and a reference about the soft clustering method, hoping that it is concise but helpful (lines 101-106).

- Page 8, paragraph 2, lines 157-161; I suggest to explain in depth the coding of clinical management and connect it with the data that present on page 10, paragraph 2, lines 200-204.

We have added a sentence explaining the purpose of registering this variable, which connects with the section of the multimorbidity cluster analysis (lines 167-168).

- Review the use of the abbreviation (R) throughout the document (for example page 10, paragraph 2, lines 201, 207 y 215).

Thank you for pointing out the inconsistencies, which have all been revised.

- Page 10, lines 205-207; a deep explanation of this paragraph is necessary, it is not enought for understand the main idea.

We have finally decided to suppress this paragraph, as it was confusing and redundant.

- Page 11, paragraph 2, lines 227-228, review if is characterize diseases or individuals.

We have changed and simplified the sentence in order to make it more clear and avoid confusion between individuals and diseases (lines 231-232).

- Page 11, paragraph 3, line 233: Instead "a disease" "chronic conditions (CC)" and instead of “syndrome”, geriatric syndrome (GS).

Agreed, thank you for pointing it out, we have made the corresponding changes in the manuscript.

- Table 1. The variable score of clinical management was missing.

We have incorporated the descriptive data of the clinical management variable in Table 1, according to patients. This variable refers to the number of CC that have required any clinical management during the index hospitalization.

- Page 14, paragraph 2, line 274-275, Check the title of table 4 of the supplement, the information is inconsistent.

We have added a clarification on the contents of the Supplemental Table 4.

- It seems to me that the text on page 17, paragraph 4, lines 343-345 should be the main focus of the discussion.

We agree that this section should be given more importance and have therefore moved it up in the discussion section, along with some changes and additions to emphasize it (lines 318-326).

Reviewer: 2
Dr. M Polidori, Universitat zu Koln

Comments to the Author:

The work presented is related to a certainly highly important topic, i.e. that of multimorbidity clustering with advancing age and its profiling as far as presence of geriatric syndromes is concerned. While a very careful analysis of the observations yields a good deal of potentially relevant, clinically useful data for better management of older inpatients, the authors appear to have missed the very core of their results - so that the paper in its present form seems largely confirmatory, quite aspecific and not really vehicle of practical implication for the readers. Several premises, instruments, endpoints and conclusions indicate lack of familiarity with the topic of aging medicine and unfortunately deeply twist the whole picture. First of all, the focus of the work since its design is tightly kept on multimorbidity and chronological age, which completely obfuscates the true patient-centered approach (term used by the authors but unfortunately not applied in their study): multidimensional, comprehensive evaluation beyond organ disease, evaluation and management of the impairment of intrinsic capacity and close value-based assessment of quality of life. Accordingly, the authors chose to scale patients' chronic conditions based on the level of clinical management required both at admission and during hospitalization instead than based on the impact on patients' quality of life. This way, the authors shifted the attention from the patient to the management needed, thereby missing critical information for the purpose of their study. For example, Cluster 3 will typically cause less management effort but negatively impact on quality of life and very often induce the onset or worsening of several geriatric syndroms including isolation, cognitive decline and instability. As a (an important) corollary, it is very difficult to understand that the CM score was given on a subjective, i.e. not validated basis and that no standardized method of assessment was used to diagnose geriatric syndromes. Additionally, not only frailty was categorised as a geriatric syndrom in spite of recent developments, but this very central feature of older inpatients was diagnosed with highly dishomogeneous methods very poorly capturing complexity of frailty and therefore its presence and severity degree.

One relevant limitation is that the fundamental source of critical information for the medical community, i.e. Table 4, fully escapes discussion. Important information on the number and nature of geriatric syndromes present in each cluster might offer to healthcare practitioners a path to access a great number of factors strongly influencing patients' trajectories but systematically escaping diagnostic algorithms and codes in real life.

The style should be adjusted and some generic expressions (like "makes sense") might be avoided.

We greatly appreciate your thoughts and reflections on such important issues in the older patients that undoubtedly should be taken into account in the clinical practice. As you well know, reality is not always what it should be. Thus, the Comprehensive Geriatric Assessment still lacks systematic implementation in the healthcare routine, although we are in the right direction and the situation experienced during the current epidemic will possibly help in the appropriate assessment and recognition of older patients.

However, our study did not intend to delve into geriatric aspects, but rather to consider multimorbidity in a cohort of older patients, also taking into account geriatric syndromes, in such a way compatible with the usual clinical practice, without changes in the care processes. It is a study based on reality, with its strengths and weaknesses, and with specific objectives and a limited budget. Obviously, we

know from experience that other aspects such as functional reserve, quality of life, social situation or degree of disability, among others, are important when making decisions –ideally shared with patients or families–. Nevertheless, these aspects are unfortunately not often assessed in an objective or standardized way or there is no evidence of it in the clinical history.

In fact, our use of the term 'patient-centred' wanted to reflect that our multimorbidity study was not limited to chronic morbidities but went a little further, also considering geriatric syndromes (and frailty), an unusual fact in the bibliography on clusters of multimorbidity in older patients, thus beginning to incorporate this perspective. Due to the lack of consideration in our study of disabilities, social needs, values, preferences or other issues that are integrated in the concept of "patient-centredness", this term has been excluded from the manuscript when referring to the analysis approach.

On the other hand, our CM variable is certainly an approximation to the weight or importance of each chronic pathology in the care episode under study. It seemed to us that, taking into account the objective of defining the patterns, and not knowing useful precedents in the consulted bibliography, the assignment made by the medical professional who attended the patient was an easy, simple measure, and shared by all professionals at the time of writing the clinical course.

It is far from our rigour to use heterogeneous criteria or not to standardize the information collection process, but that is (or was) the reality in the different participating centres, and it is based on this information (which is not as objective as it would be desirable) that decisions in clinical practice are often taken. To follow the example of frailty, in some geriatric units the usage of Frail-VIG is widespread (first published in 2017 by Amblàs et al, and composed of 22 items that include social, emotional or functional aspects, among others), but not so much in internal medicine departments. In fact, there are multiple assessment scales, and some are complex to use. Certainly, the most fragile chronic patient, as Onder G describes in Eur J Intern Med 2018, tends to have worse therapeutic results, higher rate of adverse reactions, little adherence to medication... as some examples. We agree that frailty is a nosological entity of its own that derives from a comprehensive assessment of the patient, which has an impact on chronological age, and is important for early decision-making, for example.

It is important to bear in mind that the purpose of the multimorbidity patterns in our study was not to identify needs, prognostic factors or relationships with future quality of life in patients treated in the index episode. Instead, it was to define possible subgroups or profiles of inpatients based on the burden of chronic morbidity and geriatric syndromes (including frailty although we could not ensure a standard and homogeneous measure), to then, in further analyses according to the study protocol (Baré M, BMJ Open 2020), explore the possible relationship with inappropriate prescribing, and in turn with adverse reactions to medication.

Taking your insightful comments into account, as well as the considerations we have exposed, we have made some modifications in the discussion. The paragraph about the purpose of the multimorbidity patterns has been modified and moved up (lines 318-326), the limitations section has been extended (lines 392-409), and some more emphasis has been added in the clinical implications section (lines 421-424), hoping to have covered your main concerns. Furthermore, generic expressions have been substituted to more concrete expressions.

VERSION 2 – REVIEW

REVIEWER	Mino-León, Dolores Instituto Mexicano del Seguro Social, Unidad de Investigación Médica en Epidemiología Clínica
REVIEW RETURNED	17-Sep-2021

GENERAL COMMENTS	All suggestions that were requested were carried out.

REVIEWER	Polidori, M Universitat zu Koln
REVIEW RETURNED	02-Oct-2021

GENERAL COMMENTS	The main issues have been satisfactorily addressed.