

REVISIÓN SISTEMÁTICA

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PREVALENCIA DE FRAGILIDAD EN ADULTOS MAYORES HOSPITALIZADOS.
REVISIÓN SISTEMÁTICA^(*)

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RESUMEN

Fundamentos: Existe escasa evidencia sobre la prevalencia, herramientas de medición, resultados de salud y eficacia de las intervenciones sobre la fragilidad en adultos mayores en medio hospitalario. Por ello, presentamos los resultados de una revisión sistemática de la Fragilidad en adultos mayores en medio hospitalario, siguiendo la metodología de la declaración PRISMA.

Métodos: Se encontraron 2.050 artículos en PubMed. Tras la valoración inicial de los títulos y resúmenes, lectura de texto completo y revisión de los meta-análisis, al final se incluyeron en la revisión sistemática 246 originales.

Resultados: El principal resultado fue que, de los 246 originales revisados, 179 describían la prevalencia de fragilidad en adultos mayores en el hospital, siendo el porcentaje combinado del 41,4% (IC 95% 38,4% a 44,4%; rango 4,7% a 92,5%). Por tipo de estudios predominaron los observacionales prospectivos 166 (67,5%), observacionales retrospectivos o transversales 64 (26,2%) y ensayos clínicos 15 (6,1%). Los dispositivos asistenciales más frecuentes fueron el Hospital en general/Hospitalización 125 (50,8%), Geriátría 41 (16,7%), Unidades quirúrgicas 23 (9,3%), Cardiología 18 (7,3%), Urgencias/emergencias 15 (6,1%) y otros dispositivos médicos 24 (9,8%). Las herramientas de valoración de la fragilidad más empleadas fueron la *Clinical Frailty Scale* en 69 artículos (28%), fenotipo de fragilidad en 41 (16,7%), *Frailty Index* en 39 (15,9%) y herramienta *FRAIL* en 27 (11,0%). En varios artículos se emplearon dos o más de las herramientas descritas, y en muchos, las escalas y los puntos de corte fueron arbitrariamente modificados por los autores, generando una gran heterogeneidad en los resultados.

Conclusiones: La prevalencia de fragilidad en adultos mayores en el hospital es muy alta, pero es necesaria una mayor uniformidad en su medición y la implementación de ensayos clínicos para evaluar intervenciones.

Palabras clave: Fragilidad, Hospital, Adulto mayor.

ABSTRACT

**Frailty prevalence in hospitalized older adults.
A systematic review**

Background: There is uncertain evidence regarding the prevalence, measurement tools, outcomes, and efficacy of the interventions on frailty in hospitalized older adults. For this reason, we present the results of a systematic review about Frailty and Hospital, following the PRISMA methodology.

Methods: We found 2,050 articles published in PubMed. After an initial assessment of titles and abstracts, complete comprehensive text lecture, and meta-analysis review, we finally included in the systematic review 246 originals.

Results: The main result of the systematic review is that from the 246 articles, 179 described frailty prevalence in hospital older adults, with a pooled prevalence of 41.4% (95% CI 38.4% to 44.4%; range 4.7% to 92.5%). The most frequent type of studies were those observational prospectives 166 (67.5%), being the rest observational retrospective or cross-sectional 64 (26.2%) or randomized clinical trials 15 (6.1%). The most frequent healthcare levels where the studies took place were the Hospital/Hospitalization in 125 (50.8%), Geriatric Department in 41 (16.7%), Surgical Units in 23 (9.3%), Cardiology Department in 18 (7.3%), Emergency Department in 15 (6.1%), and other in 24 (9.8%). The most frequent used measurement tools were the Clinical Frailty Scale in 69 works (28%), the frailty phenotype in 41 (15.9%), the Frailty Index in 39 (15.9%) and the FRAIL scale in 27 (11.0%). In several papers, more than one instrument was used, and in many of them, scales and cut-off points were arbitrarily determined, producing a great results heterogeneity.

Conclusions: The prevalence of frailty in hospitalized older adults is very high. It is necessary to improve frailty measure homogeneity and to realize randomized clinical trials in this population.

Key words: Frailty, Hospitalization, Older adult.

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INTRODUCCIÓN

Puede resultar sorprendente que tras 20 años de la publicación del fenotipo de fragilidad por L.P. Fried⁽¹⁾, debamos comenzar un artículo especial como éste hablando de la definición de fragilidad, pero los datos que presentamos a continuación lo hacen imprescindible. La fragilidad es definida por el último consenso de la *Joint Action* europea *ADVANTAGE* como “*un estado caracterizado por un declinar progresivo de los sistemas fisiológicos relacionado con el envejecimiento, que resulta en una reducción de la capacidad intrínseca y que confiere una extrema vulnerabilidad a estresores, aumentando el riesgo de presentar eventos adversos de salud*”⁽²⁾. Esta definición está en consonancia con la promovida por la Organización Mundial de la Salud (OMS)⁽³⁾. Con una tasa de prevalencia cercana al 18% en mayores de 65 años de la comunidad⁽⁴⁾, entre el 12% y el 24% según la herramienta empleada⁽⁵⁾ y una tasa de incidencia de 43,4 casos por 1.000 personas/año⁽⁶⁾, su verdadera importancia radica en que es un poderoso predictor de resultados graves de salud en esta población^(7,8,9,10) y mala calidad de vida⁽¹¹⁾, originando un incremento en el uso de recursos sanitarios y en los costes^(12,13).

Debe quedar claro que cualquier otra definición de fragilidad no lo es y puede conllevar a graves errores de diagnóstico y manejo y extraer conclusiones equivocadas con repercusiones negativas sobre políticas sanitarias. En este sentido hay que resaltar que fragilidad no es riesgo, y recientemente muchos autores tienden a igualarlas. Evidentemente la fragilidad supone un riesgo de eventos adversos de salud, al igual que la diabetes o la hipertensión arterial, pero nadie equipara los términos diabetes y riesgo o hipertensión y riesgo. Al igualar fragilidad con riesgo, estamos negando todo el sustrato fisiopatológico que la sustenta, estamos negando su definición, estamos modificando las herramientas de medición, estamos

difuminando las intervenciones específicas entre un maremágnum de intervenciones sobre cualquier factor de riesgo y por último, estamos obteniendo conclusiones equivocadas de los resultados de los ensayos clínicos y de los meta-análisis, que pueden influir en el diseño de políticas sanitarias, en la adecuación y utilización de recursos, y en el desarrollo de guías clínicas.

Estos problemas con la definición se agravan cuando nos introducimos en el mundo de la fragilidad en el hospital. La necesidad de identificar y estratificar de manera exacta, pero al mismo tiempo factible a los pacientes en riesgo de eventos adversos durante una hospitalización o al ingreso en urgencias, ha conducido al desarrollo de múltiples herramientas predictoras de riesgo como el *Identification of Seniors At Risk score* (ISAR)⁽¹⁴⁾, o el *Emergency room evaluation and recommendations* (ER2)⁽¹⁵⁾. El grave error metodológico aparece cuando se identifica ese riesgo de presentar eventos adversos con fragilidad, en lugar de considerar la fragilidad como un factor de riesgo independiente más a considerar, con una fisiopatología propia. Así recientemente aparecen herramientas como el *Hospital Frailty Risk Score* (HFRS)⁽¹⁶⁾, que identifica como frágil a la persona mayor en riesgo de eventos adversos, sea por el motivo que sea. Por ejemplo, es bien conocido que fragilidad y multimorbilidad, aunque son condiciones asociadas, no son lo mismo, ya que la mayoría de los sujetos frágiles, el 72%, tienen multimorbilidad, pero solo una pequeña parte de aquellos con multimorbilidad, el 16%, son frágiles⁽¹⁷⁾. Otro error en la identificación de pacientes frágiles, posiblemente todavía peor y que se está también cometiendo, es igualarlos a alteraciones en biomarcadores de laboratorio, puesto que dichos parámetros se asocian con peores resultados de salud. Esto ocurre con herramientas como el *FI-Lab21*⁽¹⁸⁾. Es lógico pensar que pacientes hospitalizados con peor función renal o hepática tengan peores resultados de salud, pero, ¿es esto fragilidad?

Es conocido que la hospitalización conlleva asociadas una serie de condicionantes que hacen que la medición de la fragilidad sea difícil de realizar con las herramientas empleadas en ámbito comunitario, pero ello no debe hacernos caer en la fácil solución de decir que bien “*no se puede*”, bien “*diseño una escala nueva como el EmSFI⁽¹⁹⁾, modifíco o adapto una previa como el FRESH-screening⁽²⁰⁾*” o bien “*llamemos fragilidad a otra cosa*”. Si bien es cierto que la fragilidad toma especial relevancia en ámbitos comunitarios, es de gran relevancia que sea identificada en el hospital como factor de riesgo preeminente. Para ello solo existen dos soluciones, la primera y mejor es que el paciente acuda al hospital con una determinación previa de su estado de fragilidad por parte de Atención Primaria, y la segunda y peor, es que definamos cuál es la mejor herramienta que identifica fragilidad en el ámbito hospitalario. Por último, no podemos olvidar las enormes diferencias de atención sanitaria a los mayores según el ámbito hospitalario en el que nos movamos, urgencias, consultas externas, hospitalización, críticos o unidades quirúrgicas. Es muy posible que cada ámbito deba tener sus peculiaridades en la determinación de la fragilidad, aunque insistimos, la mejor solución siempre será la determinación sistemática del estado de fragilidad desde Atención Primaria, y que el paciente entre en el hospital con su estado de fragilidad medido, al igual que ocurre con otros factores de riesgo como la diabetes, la dislipemia o la hipertensión arterial.

No menos importante resulta el llamativo olvido por parte de la OMS y otros organismos internacionales de la importancia que tienen la fragilidad y otros constructos afines como la capacidad intrínseca o la capacidad funcional⁽²¹⁾ durante una hospitalización. Es bien conocido que entre los mayores hospitalizados, la fragilidad se ha asociado con eventos adversos de salud como prolongación de la estancia hospitalaria, reingresos no programados,

delirium, caídas y sobre todo por su relevancia, discapacidad sobrevenida, mala calidad de vida y muerte⁽²²⁻³¹⁾. Estas consecuencias se agravan cuando, además, no se adoptan intervenciones específicas para prevenirlas y/o tratarlas⁽³²⁾. Por ello, olvidar la fragilidad en ámbito hospitalario solo ayudará a mantener un sistema hospitalario anticuado, inadecuado a su principal usuario que es el adulto mayor, continuando con la generación de discapacidad sobrevenida tras una hospitalización^(31,33).

Por último, pero no menos importante, fragilidad y hospital tienen una estrecha relación tri-direccional, ya que en primer lugar la fragilidad es un predictor independiente de hospitalización^(34,35) y reingresos hospitalarios⁽³⁶⁾, en segundo lugar, la fragilidad aumenta el riesgo de eventos negativos durante una hospitalización y al alta^(37,38), y el hospital es además un potente productor de fragilidad sobrevenida⁽³³⁾.

Ante este acúmulo de retos sin resolver, nos propusimos realizar una revisión sistemática de la literatura para conocer los trabajos publicados sobre fragilidad en el hospital, en los campos de la prevalencia, asociación con otras condiciones de salud o factores sociodemográficos, biomarcadores, como factor de riesgo de eventos adversos, intervenciones o costes, y así poder identificar las líneas de trabajo futuras en este ámbito. En este artículo presentamos los datos descriptivos de la fragilidad en el hospital.

MATERIAL Y MÉTODOS

Diseño del estudio: Nuestro trabajo consistió en una revisión sistemática de la literatura. Para ello se siguió la declaración PRISMA para revisiones sistemáticas y meta-análisis⁽³⁹⁾. El protocolo fue registrado en PROSPERO.

Pregunta PICO: Describir la prevalencia de fragilidad y prefragilidad en pacientes adultos mayores hospitalizados, independiente del nivel

asistencial hospitalario y de la herramienta de medición de fragilidad empleada.

Estrategia: Para responder a la pregunta de investigación, utilizamos la base de datos PubMed. Los términos utilizados fueron “*frail**”, “*frailty*” y “*hospital**”; tanto en lenguaje libre como controlado (Mesh). Se empleó como estrategia de búsqueda la expresión (*frailty [Mesh] AND hospital* [Mesh] AND frail* [title]*) OR (*frailty [Mesh] AND frail* [title] AND hospital**).

Criterios de inclusión y exclusión: Para la presente revisión sistemática se incluyeron todos los artículos incluidos en PubMed hasta el 28 de Julio de 2021 y que trataran sobre pacientes adultos mayores de 65 años frágiles en ámbito de hospitalización, incluyendo urgencias, encamación médica y quirúrgica o en unidades de críticos.

Se incluyeron cualquier tipo de estudio, como ensayos clínicos controlados, meta-análisis, u observacionales que determinaban fragilidad en el ámbito hospitalario. Se incluyeron los artículos en adultos mayores, cuando la edad era ≥ 70 años para todos los participantes, o en caso de incluir pacientes más jóvenes, cuando la desviación estándar (DE) de la media o el rango intercuartílico (RIQ) de la mediana no incluían a menores de 65 años, para evitar extraer conclusiones derivadas de la hospitalización de adultos jóvenes. Solo se incluyeron artículos que emplearon herramientas de fragilidad basadas en el constructo físico^(1,40,41), o bien cuando la herramienta empleada estaba validada frente a las herramientas tradicionales como el fenotipo de fragilidad de Fried⁽¹⁾, la escala clínica de fragilidad (CFS)⁽⁴⁰⁾ o el índice de fragilidad (FI)⁽⁴¹⁾. Las herramientas aceptadas se describen en la **tabla 1**.

Se excluyeron revisiones narrativas, editoriales, casos clínicos, series de casos, estudios

en animales, resúmenes en congresos y artículos duplicados. Solo se seleccionaron artículos en lengua inglesa y española.

Proceso de selección de los artículos: La revisión de los artículos ha sido realizada por cuatro autores. Tres autores revisaron título y resumen y un cuarto autor realizó la verificación de la preselección. Seguidamente se realizó la lectura a texto completo de todos los artículos preseleccionados. Los que no cumplieran criterios o eran irrelevantes se excluyeron en esta segunda fase de selección. Los resultados de tipo de estudio meta-análisis fueron analizados con búsqueda manual para posible inclusión de nuevos artículos que cumplieran criterios.

Extracción de los datos: La extracción de datos de los estudios que fueron incluidos se realizó de manera independiente por los tres revisores iniciales (AAC, EGJ y EBCZ) en una hoja de cálculo prediseñada (Microsoft Excel[®]). Cuando existieron dudas sobre la idoneidad, se consultó con el cuarto revisor (PA). Se extrajeron los siguientes campos: Primer autor, año de publicación, tipo de estudio, país, dispositivo asistencial hospitalario, tipología de paciente según patología predominante, tamaño poblacional, edad con indicador de dispersión, herramienta para medir fragilidad, punto de corte para determinación de fragilidad y prefragilidad, prevalencia de fragilidad y prefragilidad, y resultados de salud medidos.

Análisis de la calidad: Empleamos un abordaje crítico de la evaluación para valorar la calidad global, que incluyó una descripción de los resultados y del material incluido, los criterios empleados para el procedimiento final de la selección y la metodología empleada para el procesamiento de datos.

Análisis estadístico: Se realizó un análisis descriptivo de los campos analizados. La prevalencia de fragilidad se determinó de manera

Tabla 1
Herramientas consideradas válidas para identificar fragilidad.

Acronimo	Nombre completo y referencia
Fenotipo de fragilidad	Fenotipo de fragilidad ⁽¹⁾
CFS	<i>Clinical Frailty Scale</i> (Escala clínica de fragilidad) ⁽⁴⁰⁾
FI	<i>Frailty Index</i> (Índice de fragilidad) ⁽⁴¹⁾
SHARE-FI	<i>Survey of Health Ageing and Retirement in Europe Frailty Index</i> ⁽⁴²⁾
TFI	<i>Tilburg Frailty Indicator</i> ⁴³⁾
GFI	<i>Groningen Frailty Indicator</i> ⁽⁴⁴⁾
HFRS	<i>Hospital Frailty Risk Score</i> ⁽¹⁶⁾
SUHB	<i>Scale for Stable gait/unstable gait, needing Help or being bedridden</i> ⁽⁴⁵⁾
VMS	<i>Veiligheids Management Systeem frailty score</i> ⁽⁴⁶⁾
FSI	<i>Frailty Screening Index</i> ⁽⁴⁷⁾
FI-VIG	Índice de Fragilidad basado en Valoración Geriátrica Integral ⁽⁴⁸⁾
DFI	<i>Derby Frailty Index</i> ⁽⁴⁹⁾
FI-Lab	<i>Frailty Laboratory</i> ⁽⁵⁰⁾
FI-AC	<i>Frailty Index obtenido del interRAI-Acute Care Instrument</i> ⁽⁵¹⁾
MFST	<i>Maastricht frailty screening tool</i> ⁽⁵²⁾
MPI	<i>Multidimensional Prognostic Index</i> ⁽⁵³⁾
FRAIL	<i>FRAIL instrument</i> ⁽⁵⁴⁾

conjunta para todos los estudios, y separada por herramienta principal empleada, así como por tipología de ámbito asistencial y tipología de paciente.

RESULTADOS

Se encontraron 2.050 artículos en PubMed. Tras la valoración inicial de los títulos y resúmenes, se excluyeron 1.736, quedando 314 para la lectura de texto completo (182 originales y 15 meta-análisis). La revisión de los 15 meta-análisis extrajo 64 originales que no habían sido

inicialmente identificados en la búsqueda en PubMed, por lo que al final se incluyeron en la revisión sistemática 246 originales. La **figura 1** presenta el diagrama PRISMA para la selección de los artículos, con las causas de exclusión de aquéllos que no fueron aceptados para el estudio. La tabla Excel con los resultados de los estudios se presenta como **anexo I** y las referencias bibliográficas de los 246 artículos finales incluidos y de los 15 meta-análisis se presentan en el **anexo II**.

El principal resultado de la revisión sistemática es que, de los 246 originales revisados,

Figura 1
Identificación de estudio.

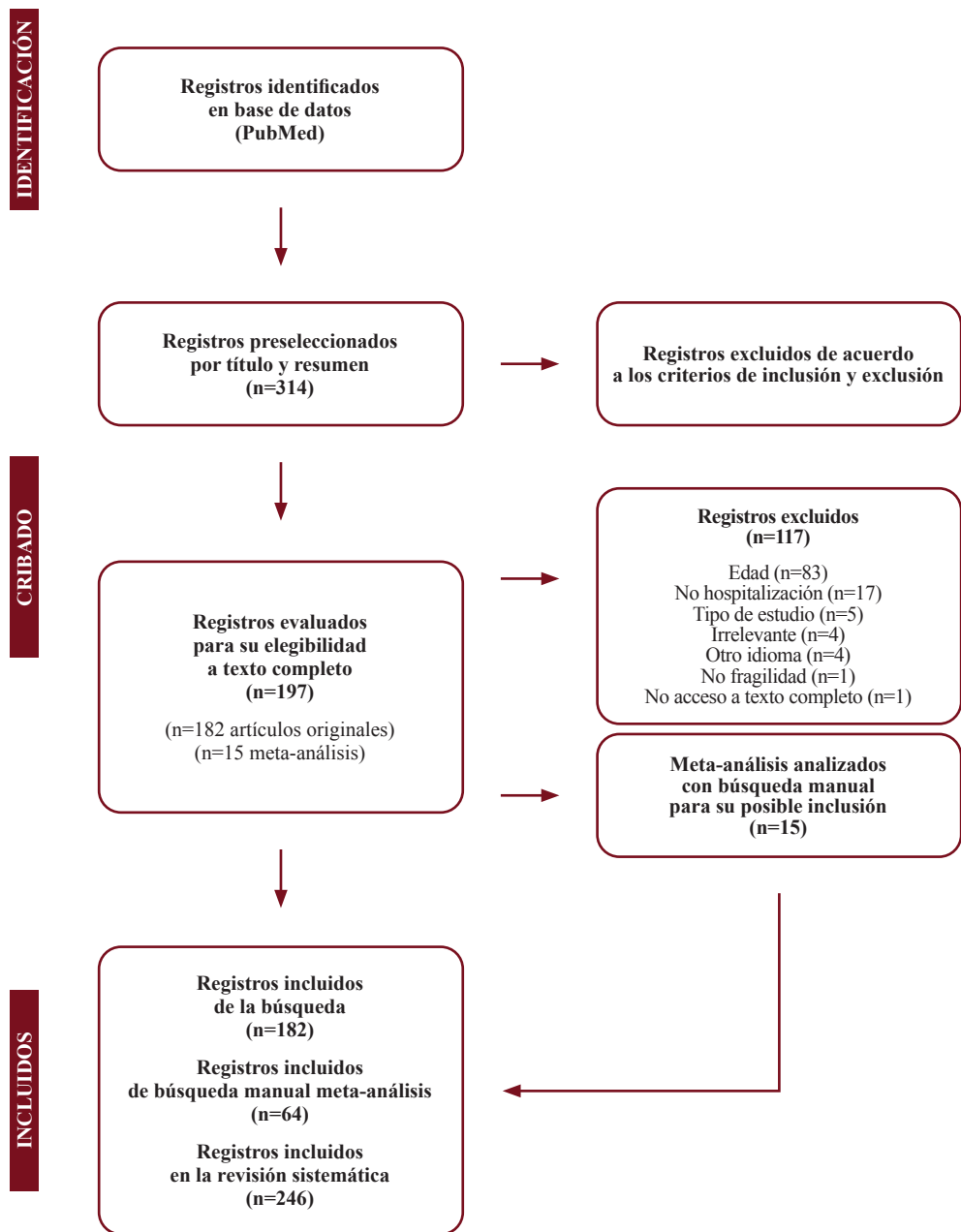


Figura 2
Clasificación del Continuum Funcional (FCS).

Categoría	ABVD	AIVD	Fragilidad	Constructo	Mortalidad a 5 años (%)	Mortalidad a 10 años (%)
1	Independiente	Independiente	No frágil	Barthel \geq 90, Lawton = 8 0 criterios fenotipo fragilidad	1,3	15,8
2	Independiente	Discapacidad	No frágil	Barthel \geq 90, Lawton < 8 0 criterios fenotipo fragilidad	10,5	26,6
3	Independiente	Independiente	Pre-frágil	Barthel \geq 90, Lawton = 8 1-2 criterios fenotipo fragilidad	6,9	22,4
4	Independiente	Discapacidad	Pre-frágil	Barthel \geq 90, Lawton < 8 1-2 criterios fenotipo fragilidad	23,2	49,7
5	Independiente ABVD		Frágil	Barthel \geq 90 \geq 3 criterios fenotipo fragilidad	38,8	62,0
6	Discapacidad leve para ABVD			Barthel 85-60	51,2	75,0
7	Discapacidad moderada para ABVD			Barthel 55-40	75,0	89,6
8	Discapacidad grave para ABVD			Barthel < 40	78,8	97,1

ABVD: Actividades básicas de la vida diaria; AIVD: actividades instrumentales de la vida diaria.

179 describían la prevalencia de fragilidad con cualquiera de las herramientas aceptadas y descritas en la tabla 1. El porcentaje combinado de fragilidad fue del 41,4% (IC 95% 38,4% a 44,4%; Rango 4,7% a 92,5%).

El tipo de estudios fue en su mayoría observacional prospectivo 166 (67,5%) y el resto fueron observacionales retrospectivos o transversales 64 (26,2%), ensayos clínicos 15 (6,1%) y 1 no clasificable (0,4%). Por países de autoría/realización, los más frecuentes fueron Estados Unidos con 36 estudios, China con 29, Reino Unido con 25, España con 21, Canadá con 19, Australia con 14 y Japón con 10. El dispositivo asistencial fue por orden de frecuencia el Hospital en general/Hospitalización 125 (50,8%), Geriatria 41 (16,7%), Unidades quirúrgicas 23 (9,3%), Cardiología 18 (7,3%), Urgencias/emergencias 15 (6,1%) y otros dispositivos médicos 24 (9,8%). Las herramientas de valoración de la fragilidad más empleadas en los estudios fueron la *Clinical Frailty Scale* en 69 artículos (28,0%), el fenotipo de

fragilidad de Fried en 41 (16,7%), el *Frailty Index* en 39 (15,9%) y la herramienta *FRAIL* en 27 (11,0%). Hay que remarcar que en varios artículos se empleaban dos o más de las herramientas descritas, y que, en muchos artículos, las escalas y los puntos de corte fueron arbitrariamente modificados por los autores, generando una gran heterogeneidad en los resultados.

DISCUSIÓN

La primera lectura que debe hacerse de este meta-análisis es que la prevalencia de fragilidad en el medio hospitalario es muy alta, del 41,4%, independientemente de la herramienta de medición empleada o del dispositivo asistencial en el que nos encontremos. Aunque la fragilidad es un problema relevante en el ámbito comunitario, que ha llevado a la creación de una *Estrategia Nacional de Salud para la Prevención de la Fragilidad y las Caídas*⁽⁵⁵⁾, nuestros resultados son una llamada de atención a que el reto de la fragilidad debe ser también abordado desde la perspectiva

hospitalaria. De hecho, cada vez encontramos un mayor número de editoriales reflejando la necesidad de medir fragilidad en pacientes hospitalizados, no solo desde el ámbito de la geriatría, sino desde otros ámbitos tan diferentes como la hepatología⁽⁵⁶⁾, la cardiología⁽⁵⁷⁾ o la anestesiología⁽⁵⁸⁾. Esto refleja nada más y nada menos que la necesidad que tienen los especialistas que tratan pacientes mayores en el hospital, de identificar fragilidad y manejar a sus pacientes de manera diferenciada y especializada acorde a las características funcionales de los adultos mayores⁽⁵⁹⁾. En este sentido, recientemente nuestro grupo ha diseñado una herramienta, la Clasificación del Continuum Funcional (FCS), que concilia la fragilidad y la discapacidad en una única escala progresiva, entendiendo fragilidad como un estado prediscapacidad (figura 2). La Clasificación del Continuum Funcional identifica adecuadamente no solo mortalidad a los 10 años⁽⁶⁰⁾, sino también hospitalizaciones durante ese periodo de tiempo⁽⁶¹⁾, pudiendo ser una herramienta de interés en población hospitalaria.

La segunda reflexión es que 20 años después del fenotipo de fragilidad, la fragilidad en el medio hospitalario se sigue midiendo de manera dispar, con multitud de herramientas con poca relación entre ellas, probablemente identificando diferentes constructos, lo que conlleva a los clínicos a incertidumbre y al desánimo^(62,63). Las diferentes escalas producen valores diferentes en la prevalencia, en la factibilidad de su uso, en los resultados de salud, y además presentan una pobre concordancia entre ellas sugiriendo que miden constructos de fragilidad diferentes⁽⁶³⁾.

En tercer lugar, es llamativo que la mayoría de los estudios son observacionales, describiendo prevalencia y resultados de salud, habiendo encontrado en la revisión sistemática solamente 15 ensayos clínicos referentes a intervenciones en pacientes frágiles. Más aún, de las 15

revisiones sistemáticas/meta-análisis encontrados, ninguno fue de ensayos clínicos o intervenciones, siendo todos de estudios descriptivos. Esto puede significar que estamos en fases todavía iniciales de la implementación de la medida de la fragilidad como ítem importante en los pacientes mayores hospitalizados, pero creemos ya llegado el momento de superar esta fase de estudios, necesarios en un primer momento, para pasar a la fase de estudios de intervención y ensayos clínicos. Ya conocemos que la fragilidad a nivel hospitalario se asocia con mayor mortalidad, discapacidad, institucionalización, morbilidad, complicaciones postoperatorias o estancia media prolongada, por lo que ha llegado el momento de la intervención. Valoración Geriátrica Integral⁽⁶⁴⁾, ejercicio^(65,66), nutrición⁽⁶⁷⁾, manejo de la polifarmacia⁽⁶⁸⁾ y manejo por equipos especializados en los que el geriatra y la enfermera especialista en geriatría tienen un papel predominante^(69,70,71), son las intervenciones más testadas y con mejores resultados ante esta población.

Como conclusión de esta revisión sistemática, parece evidente la elevada prevalencia de fragilidad en el medio hospitalario, y que es necesaria una mayor uniformidad en su medición y la implementación de ensayos clínicos para evaluar intervenciones. En un próximo meta-análisis basándonos en la revisión sistemática realizada, analizaremos la asociación de la fragilidad con eventos adversos de salud.

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ANEXO I: BIBLIOGRAFÍA DE LOS ESTUDIOS SELECCIONADOS

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ANEXO II: REFERENCIAS DE LOS 15 META-ANÁLISIS Y ARTÍCULOS SELECCIONADOS A PARTIR DE ELLOS

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