TESIS DE LA UNIVERSIDAD DE ZARAGOZA
2021
92

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Avances en pancreatitis aguda: Clasificaciones e influencia de la dieta y las características basales de los pacientes en su evolución clínica

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ISSN 2254-7606

Prensas de la Universidad
Universidad Zaragoza

ISSN 2254-7606

Universidad Zaragoza
1542

Tesis Doctoral

AVANCES EN PANCREATITIS AGUDA: CLASIFICACIONES E INFLUENCIA DE LA DIETA Y LAS CARACTERÍSTICAS BASALES DE LOS PACIENTES EN SU EVOLUCIÓN CLÍNICA

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UNIVERSIDAD DE ZARAGOZA
Escuela de Doctorado

Programa de Doctorado en Medicina

2020

Departamento de Medicina, Psiquiatría y Dermatología

UNIVERSIDAD DE ZARAGOZA
U. Z.

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Memoria presentada por D. Guillermo García Rayado para optar al título de Doctor

2020

Este trabajo ha sido posible gracias a la financiación del Instituto de Salud Carlos III (Contrato de investigación CM17/00145), el CIBER de enfermedades hepáticas y digestivas (CIBERehd), y el Gobierno de Aragón mediante la concesión de subvenciones a la actividad investigadora de los grupos reconocidos por el Gobierno de Aragón (Grupo de Patología Digestiva del Instituto de Investigación Biosanitaria Aragón B-01)

El licenciado en Medicina D. Guillermo García Rayado solicita la presentación de su tesis doctoral como compendio de publicaciones con unidad temática en "Pancreatitis Aguda". Para ello hace constar las referencias completas de los artículos que constituyen el cuerpo de la tesis:

1. Sternby H, Bolado F, Canaval-Zuleta HJ, Marra-López C, Hernando-Alonso AI, Del-Val-Antoñana A, García-Rayado G, Rivera-Irigoin R, Grau-García FJ, Oms L, Millastre-Bocos J, Pascual-Moreno I, Martínez-Ares D, Rodríguez-Oballe JA, López-Serrano A, Ruiz-Rebollo ML, Viejo-Almanzor A, González-de-la-Higuera B, Orive-Calzada A, Gómez-Anta I, Pamies-Guilabert J, Fernández-Gutiérrez-Del-Álamo F, Iranzo-González-Cruz I, Pérez-Muñante ME, Esteba MD, Pardillos-Tomé A, Zapater P, de-Madaria E. Determinants of Severity in Acute Pancreatitis: A Nation-wide Multicenter Prospective Cohort Study. Ann Surg. 2019 Aug;270(2):348-355. doi: 10.1097/SLA.0000000000002766. PMID: 29672416.

   Factor de Impacto: 9,476. Primer decil.

2. Moran RA, García-Rayado G*, de la Iglesia-García D, Martínez-Moneo E, Fort-Martorell E, Lauret-Braña E, Concepción-Martín M, Ausania F, Prieto-Martínez C, González-de-Cabo M, Quesada-Vázquez N, Marcaide-Ruiz-de-Apodaca MA, Pajares-Díaz JA, Díaz FC, de-Benito JL, Hinojosa-Guadix J, Marqués-García P, Boadas J, Bajador-Andreu E, Moreno O, Argüelles-Arias F, Martín-Benítez G, Tafur-Sánchez C, Leal-Téllez J, Romero-Mosquera B, Hernaez R, Papachristou GI, Singh VK, de-Madaria E. Influence of age, body mass index and comorbidity on major outcomes in acute pancreatitis, a prospective nation-wide multicentre study. United European Gastroenterol J. 2018 Dec;6(10):1508-1518. doi: 10.1177/2050640618798155. Epub 2018 Sep 3. PMID: 30574321; PMCID: PMC6297924.

   * Co-primer autor

   Factor de Impacto: 3,453. Segundo cuartil.

3. García-Rayado G, Varela-Moreiras G, Lanas Á, Ferrández Á, Balza-Lareu N, Cervera JI, Bodenlle-Bello MP, Argüelles-Arias AM, Latorre P, Udaondo-Cascante MA, Soria-de-la-Cruz MJ, Lariño-Noia J, García-Figueiras R, Gil-García-Ollauri C, Ituarte-Uriarte R, Rosales-Alexander CL, Soriano J, Rodríguez-Peláez M, Mesa-Álvarez A, Oblitas E, Menso MM, Bertoletti F, Rodríguez-Prada JI, Guzmán-Suárez S, Closa D, de-Madaria E. Dietary Fat Patterns and Outcomes in Acute Pancreatitis in Spain. Front Med (Lausanne). 2020 Apr 9;7:126. doi: 10.3389/fmed.2020.00126. PMID: 32328495; PMCID: PMC7160296.
   Factor de Impacto: 3,113. Primer cuartil.

4. García-Rayado G, Cárdenas-Jaén K, de-Madaria E. Towards evidence-based and personalised care of acute pancreatitis. United European Gastroenterol J. 2020 May;8(4):403-409. doi: 10.1177/2050640620903225. Epub 2020 Jan 22. PMID: 32213025; PMCID: PMC7226696.
   Factor de Impacto: 3,453. Segundo cuartil.

Factor de Impacto total: 19,495

En Zaragoza a 16 de julio de 2020

Fdo. Guillermo García Rayado

Tabla de contenidos

Introducción

1. Perspectiva histórica

La primera mención sobre una pancreatitis aguda fue publicada en 1579 por *Iacobo Auberto Vindone* quien describió un páncreas con necrosis durante la autopsia de un paciente alcohólico [1]. Posteriormente en 1652, *Nicholaes Pietrez Tulp* publicó una descripción de un absceso pancreático en un varón con dolor de espalda y fiebre que acabó falleciendo [2]. Durante este siglo y el siguiente se publicaron varios casos describiendo necrosis pancreáticas en autopsias de pacientes fallecidos tras un dolor intenso en hemiabdomen superior. Más tarde, en 1803, *Antoine Portal* relacionó por primera vez un páncreas gangrenoso con la litiasis biliar [3]. En las décadas posteriores también se relacionó la inflamación y la necrosis pancreática con el consumo de alcohol, acuñándose el término de "páncreas de los borrachos" [1]. Pero fue en 1842 cuando *Karl von Rokitansky* estableció por primera vez la pancreatitis aguda (PA) hemorrágica como entidad propia [4]. Posteriormente en 1889, *Reginald Herber Fitz* describió los signos y síntomas de la PA así como sus diferentes etapas en un artículo que publicó en la revista *Boston Medical and Surgical Journal* (embrión de la actual *New England Journal of Medicine*) [5]. En 1908, *Julius Wohlgemuth* halló un método para determinar la concentración de amilasa en suero y posteriormente en 1925 *Gerhardt Katsch* estableció la cuantificación de la amilasa y lipasa en suero para el diagnóstico bioquímico de la PA [6]. En las décadas siguientes se continuaron realizando avances en la descripción, clasificación, diagnóstico y tratamiento de la PA hasta llegar al conocimiento actual sobre esta interesante entidad que resumimos en los siguientes apartados.

2. Fisiopatología

El páncreas es un órgano con una función doble, endocrina y exocrina. La función exocrina consiste en la producción de las principales secreciones digestivas por parte de las células acinares (secreción rica en enzimas) y ductales (secreción de agua y bicarbonato) pancreáticas. Una enzima clave es la tripsina que es secretada por las células acinares en forma de su precursor inactivo (también llamado zimógeno) llamado

tripsinógeno [7]. En el funcionamiento normal del páncreas, el tripsinógeno alcanza el duodeno y es activado y convertido a tripsina por la enzima enteroquinasa, localizada en la membrana apical de los enterocitos. El primer paso en la patogénesis de la PA es el daño de las células acinares por diferentes agentes que se explicarán en el apartado posterior *Etiología*. La lesión de los acinos pancreáticos tiene importantes consecuencias que describimos a continuación [8]:

1. Alteración de la señalización mediada por el calcio: se produce un pico de calcio en el citosol de las células que provoca la activación intracelular del tripsinógeno a tripsina [9].
2. Necrosis celular que provoca liberación de sustancias que activan la inflamación local y sistémica conocidas como "patrones moleculares asociados al daño" (*DAMPS: damage-associated molecular patterns*).
3. Producción de factores nucleares de transcripción pro-inflamatorios como el NF-kappa B [10] que a su vez inducen la secreción de moléculas pro-inflamatorias como citoquinas.
4. Bloqueo de la autofagia que conduce a la activación del tripsinógeno y a la muerte celular.

La activación intrapancreática prematura de los zimógenos a sus formas activas como en el caso de la tripsina, produce una reacción en cascada que conduce a la disfunción mitocondrial y a la autodigestión del páncreas y los tejidos circundantes que se inflaman o necrosan.

Otro evento clave en la patogénesis de la PA es la liberación de ácidos grasos insaturados mediante la hidrólisis de los triglicéridos de la grasa retroperitoneal producida por la enzima pancreática lipasa. En estudios *in vitro* e *in vivo* en animales [11-13] se ha demostrado que estos ácidos grasos insaturados libres son capaces de aumentar la necrosis pancreática localmente, pero además tras su liberación al torrente circulatorio producen toxicidad sistémica. Estudios observacionales en humanos también parecen apoyar un efecto tóxico de los ácidos grasos insaturados en pacientes con PA [14]. En cambio, la liberación de ácidos grasos saturados no produce tal efecto tóxico. Teniendo en cuenta esta diferencia y que la composición de la grasa corporal incluyendo la grasa pancreática está influenciada por el tipo de grasa ingerido [15,16],

se podría hipotetizar que diferencias en el patrón de consumo de grasas podrían conllevar diferente evolución de la PA. Este es un aspecto poco estudiado en la literatura y que será uno de los objetivos de esta tesis doctoral.

En conclusión, la activación de las enzimas pancreáticas dentro de la propia glándula produce daño local en forma de inflamación y en ocasiones necrosis pancreática y de la grasa retroperitoneal, pero también toxicidad sistémica que puede conducir al desarrollo de fallo orgánico (FO). Las diferentes complicaciones locales y tipos de FO asociados a la PA se detallarán en el apartado posterior *Historia Natural y Complicaciones.*

3. Epidemiología y etiología

3.1 Epidemiología

La PA es una de las enfermedades digestivas más frecuentes y su incidencia ha aumentado en las últimas décadas. Su incidencia actual se sitúa en torno a 14 - 45 casos por 100.000 personas/año [17]. La PA es la tercera causa más frecuente de ingreso hospitalario por enfermedad gastrointestinal, el décimo diagnóstico gastrointestinal más común en los Servicios de Urgencias y la décima causa de mortalidad por enfermedad digestiva no neoplásica [18]. Además, aproximadamente el 25% de los casos sufren una o varias recurrencias. La incidencia global es similar en ambos sexos, aunque la etiología alcohólica es más predominante en el sexo masculino y la etiología litiásica es discretamente más frecuente en el sexo femenino [19].

3.2 Etiología

Las etiologías más frecuentes de la PA son la litiasis biliar y el consumo de alcohol. Otras etiologías menos frecuentes se resumen en la *Tabla 1*.

La litiasis biliar es la principal causa de PA en España [20]. El paso de un cálculo biliar a través de la unión biliopancreática, tramo común final en el que el colédoco y el conducto pancreático principal se unen antes de su desembocadura en el duodeno,

puede producir una obstrucción y desencadenar la PA. Se han descrito algunos factores de riesgo para el desarrollo de litiasis biliar como la etnicidad (nativos Americanos), la edad avanzada, el sexo femenino, la obesidad, la pérdida rápida de peso y la nutrición parenteral total entre otros. El sexo femenino, la edad mayor de 50 años y el incremento de los niveles de ALT al ingreso son factores predictores independientes de etiología biliar de la PA [21].

El consumo de alcohol es la segunda causa más frecuente de PA. Para poder producir una PA el consumo debe ser importante (al menos 4-5 bebidas alcohólicas al día) y prolongado. Un porcentaje considerable de pacientes tras un primer episodio de PA alcohólica presentarán episodios recurrentes (en torno al 40%) y progresión hacia pancreatitis crónica (aproximadamente un 28%) [22]. El consumo de tabaco y algunos factores genéticos son cofactores relevantes en el desarrollo de pancreatitis alcohólica.

Tabla 1. Etiologías de la PA.

Patogénesis	Etiología
Obstrucción	-Litiasis biliar -Tumores pancreáticos y periampulares -Estenosis post-necrótica del Wirsung -Disfunción del esfínter de Oddi -Páncreas divisum (controvertido)
Toxicidad, alergia	-Alcohol, tabaco -Veneno de escorpión -Medicamentos como ácido valproico, azatioprina, diclofenaco…
Enfermedades metabólicas	-Hipertrigliceridemia -Hipercalcemia
Infecciones	-Virus de las hepatitis A, B y E -Citomegalovirus -Otras infecciones víricas, bacterianas y fúngicas
Iatrogénica	-CPRE -Biopsia pancreática -Cirugía
Genética	-Mutaciones de PRSS-1, CFTR, SPINK-1 y CTRC
Otras	-Pancreatitis autoinmune -Trasplante renal -Diálisis -Traumatismo

CPRE: Colangiopancreatografía retrógrada endoscópica, PRSS-1: Gen del tripsinógeno catiónico, CFTR: Cystic fibrosis transmembrane regulator gene, SPINK-1: Serine protease inhibitor Kazal type 1 gene, CTRC: Chymotrypsin C gene.
Modificado de Fast Facts: Acute and Recurrent Pancreatitis, Enrique de-Madaria and Matthias Löhr. Karger Publishers Limited. En prensa, 2020.

4. Diagnóstico

4.1 Signos y síntomas

La mayoría de los pacientes se presentan con dolor abdominal epigástrico intenso irradiado hacia los hipocondrios/flancos y/o hacia la espalda, acompañado de náuseas y vómitos. El desarrollo de ictericia puede darse en los casos con coledocolitiasis persistente asociada o menos frecuentemente en pacientes con compresión del colédoco por inflamación y/o colecciones pancreáticas. La existencia de fiebre y escalofríos al inicio del cuadro sugiere una colangitis aguda asociada. Menos frecuentemente los pacientes con PA pueden desarrollar equimosis de la piel a nivel periumbilical (signo de *Cullen*) o en los flancos (signo de *Grey Turner*).

4.2 Análisis sanguíneos y de orina

La gran mayoría de los pacientes con PA presentan una elevación de los niveles séricos de amilasa y/o lipasa. Cuanto mayor sea esta elevación, mayor especificidad diagnóstica. La amilasa se eleva a las 2-12 horas desde el inicio de los síntomas, presenta un pico a las 12-72 horas y puede mantenerse elevada hasta 5 días. La lipasa se eleva a las 4-8 horas desde el inicio de los síntomas, presenta un pico a las 24 horas y vuelve a la normalidad a los 8-14 días [23]. Existen además marcadores urinarios de PA como el tripsinógeno-2 urinario y la amilasa urinaria que pueden emplearse cuando los niveles de amilasa y lipasa en sangre puedan ser falsamente negativos como en el caso de una hipertrigliceridemia importante. Además, existen causas de dolor abdominal con elevación de la amilasa sérica diferentes a la PA y donde un diagnóstico diferencial es necesario como la colangitis aguda, colecistitis aguda, perforación, isquemia mesentérica aguda, enfermedades ginecológicas, etc. [24].

4.3 Pruebas de imagen

El TAC abdominal es la mejor prueba de imagen para el diagnóstico de PA, seguido de la RMN (aunque esta última está menos disponible). Sin embargo, el TAC y/o la RMN no son necesarios para el diagnóstico de la mayoría de los casos de PA y su realización debe reservarse para los casos con duda diagnóstica por síntomas atípicos y/o sin incremento de los niveles séricos de amilasa o lipasa. Además de para el diagnóstico

inicial, el TAC y la RMN son útiles para el diagnóstico posterior de complicaciones locales de la PA y para el diagnóstico etiológico.

4.4 Criterios diagnósticos de PA

Para el diagnóstico de PA es necesario cumplir al menos dos de los siguientes tres criterios según la clasificación revisada de Atlanta [25]:

1. Inicio agudo de dolor abdominal epigástrico intenso con frecuencia irradiado a espalda.
2. Niveles de amilasa o lipasa al menos tres veces mayores del límite alto de la normalidad
3. Hallazgos típicos de PA en las pruebas de imagen (en el TAC abdominal, y menos frecuentemente en la RMN o ecografía abdominal).

Uno de los objetivos de esta tesis doctoral será realizar una revisión bibliográfica de los principales aspectos de la PA incluido la estrategia diagnóstica.

5. Historia natural, complicaciones y clasificaciones

Dos tercios de los pacientes con PA desarrollan un curso leve de la enfermedad con una rápida recuperación, sin embargo, un tercio desarrollará complicaciones locales y/o FO. En los pacientes con PA con complicaciones locales y/o FO se distinguen dos fases [25]: A) una fase temprana en la primera semana en la que la liberación de agentes pro-inflamatorios por el daño tisular puede conducir a la aparición de un síndrome de respuesta inflamatoria sistémica (SRIS) y de FO; y B) una fase tardía a partir de la primera semana en la que predominan los síntomas secundarios a las complicaciones locales, en cuyo peor escenario éstas se infectan.

5.1 Complicaciones locales

Se distinguen dos tipos de PA, la intersticial y la necrosante. En la PA intersticial el páncreas está aumentado de tamaño debido al edema inflamatorio, pero no existe

necrosis del parénquima pancreático ni de la grasa que rodea al páncreas. Algunos pacientes con PA intersticial pueden presentar colecciones líquidas agudas peripancreáticas que son colecciones homogéneas (sin restos necróticos), sin pared definida y que se desarrollan en las primeras 4 semanas desde el inicio de la PA. La mayoría de estas colecciones se reabsorben, las que persisten más de 4 semanas y desarrollan una pared definida de tejido de granulación se denominan pseudoquistes [25].

La PA necrosante se caracteriza por la presencia de necrosis pancreática y/o peripancreática. En las primeras 4 semanas de una PA necrosante frecuentemente se forman colecciones agudas necróticas que son colecciones sin pared definida y heterogéneas por la presencia de líquido y restos necróticos. Si persisten más de 4 semanas y adquieren una pared definida se denominan necrosis encapsuladas [25].

5.2 Fallo orgánico (FO)

El FO en el contexto de la PA se define según la clasificación revisada de Atlanta mediante el sistema de puntuación de *Marshall* modificado. Según este sistema se define el FO si el paciente tiene 2 o más puntos en alguno de sus apartados, lo que equivale concretamente a: A) un cociente PaO2/FiO2 menor o igual de 300 a nivel respiratorio, B) una creatinina sérica mayor o igual a 1.9 mg/dl a nivel renal, y/o C) una presión arterial sistólica menor de 90 mmHg a nivel cardiovascular [26].

El FO puede ser transitorio si la duración es menor o igual a 48 horas o persistente si la duración es mayor de 48 horas. Por otra parte, el FO se considera único si sólo está afectado un sistema o múltiple si está afectado más de un sistema.

5.3 Clasificaciones de gravedad

Aunque hubo intentos previos, el primer gran consenso de clasificación en PA ampliamente aceptado y utilizado fue la clasificación de Atlanta publicada en 1993 [27]. Esta clasificación dividía las PA en leves si no presentaban complicaciones locales ni

FO y en graves si presentaban complicaciones locales y/o FO. Posteriormente en los años 2012 y 2013 dos nuevas clasificaciones fueron publicadas, la clasificación basada en determinantes (DBC) y la clasificación revisada de Atlanta (RAC). La DBC [28] estableció cuatro categorías de gravedad en función de la presencia de necrosis pancreática (a su vez sub-clasificada como estéril o infectada) y la presencia de FO y su duración (transitorio o persistente) (*Tabla 2*). La RAC [25] definió tres categorías: leve (no complicaciones locales ni FO), moderadamente grave (complicaciones locales y/o exacerbación de comorbilidad previa y/o FO transitorio) y grave (FO persistente) (*Tabla 3*).

Uno de los objetivos de esta tesis doctoral será validar las diferentes clasificaciones de gravedad en PA y establecer qué complicaciones locales y fallos orgánicos se asocian con una peor evolución de la PA.

Tabla 2. Clasificación basada en determinantes [28].

	Leve	**Moderada**	**Grave**	**Crítica**
Necrosis pancreática	No y No	Estéril y/o Transitorio	Infectada o Persistente	Infectada y Persistente
Fallo orgánico				

Tabla 3. Clasificación revisada de Atlanta [25].

Categoría	**Definición**
Leve	No complicaciones ni FO
Moderadamente grave	Complicaciones locales y/o complicaciones sistémicas* y/o FO transitorio
Grave	FO persistente

*Complicación sistémica: Exacerbación de comorbilidad previa.

FO: Fallo orgánico.

6. Pronóstico de gravedad

Como se ha comentado previamente, la mayoría de los pacientes con PA presentarán un curso leve de la enfermedad, pero un tercio desarrollarán una evolución tórpida con complicaciones locales y/o FO. Históricamente ha habido un gran interés en predecir de forma temprana qué pacientes desarrollarán esta peor evolución con el objetivo de poder monitorizarlos más estrechamente y detectar y tratar más precozmente el FO. Han sido estudiados factores pronósticos en relación con las características basales de los pacientes, signos clínicos, marcadores analíticos y hallazgos en las pruebas de imagen.

En cuanto a las características basales de los pacientes, la edad avanzada, la comorbilidad y la obesidad han sido asociadas con un peor pronóstico de la PA pero muchos de los estudios realizados tienen debilidades metodológicas y los resultados que aportan son dispares. Uno de los objetivos de esta tesis doctoral será establecer la influencia de la edad, la comorbilidad y la obesidad en la evolución de la PA. Los principales signos clínicos asociados a desarrollo de FO en PA son la hipoperfusión periférica, oligoanuria, taquicardia, taquipnea, cianosis y alteración del estado mental. En lo referente a los marcadores analíticos, un incremento de la urea, una elevación del hematocrito (por encima del 44%) [29] y una proteína C reactiva por encima de 150 mg/l a las 48 horas del inicio de la PA se han asociado a una peor evolución [30]. Por último, en cuanto a los hallazgos en las pruebas de imagen, la presencia de colecciones y de necrosis pancreática son los principales marcadores de gravedad y se pueden cuantificar mediante la escala del TAC (*CT score*, *Tabla 4*) [31].

Tabla 4. *CT score*.

Balthazar score		**Necrosis**	
Balthazar	Puntos	% Necrosis	Puntos
A	0	0	0
B	1	0-30%	2
C	2	30-50%	4
D	3	>50%	6
E	4		

Se asignan puntos según la escala de Balthazar y la necrosis pancreática.

Escala de Balthazar: A- páncreas normal, B: páncreas aumentado de tamaño, C: rarefacción de la grasa peripancreática, sin colecciones, D: 1 colección, E: 2 o más colecciones.

Teniendo en cuenta estos factores pronósticos e incluyendo otros adicionales se han diseñado en las últimas décadas algunos sistemas de puntuación para la predicción de gravedad en PA. Los sistemas de predicción de gravedad de *Ranson* e *Imrie* se calculan al ingreso y a los dos días posteriores lo que retrasa el resultado del score y los hace menos útiles. El sistema *APACHE-II (Acute Physiology and Chronic Health Evaluation II)* ampliamente empleado en el contexto del paciente crítico, es incómodo de calcular ya que incluye hasta 15 variables diferentes [32]. Los sistemas más utilizados actualmente son la presencia de criterios de SRIS *(Tabla 5)* sobre todo si es persistente (≥48 horas), y el sistema *BISAP (the bedside index for severity in acute pancreatitis)* que incluye la presencia de criterios SRIS, pero también otros factores como la edad mayor de 60 años, la alteración del estado mental, la elevación de nitrógeno ureico en sangre y la presencia de derrame pleural [33]. En general, estos sistemas pronósticos poseen un alto valor predictivo negativo, pero de un bajo a moderado valor predictivo positivo [34].

Tabla 5. Criterios de SRIS.

Temperatura	> a 38ºC o < a 36ºC
Frecuencia cardiaca	> a 90 latidos por minuto
Frecuencia respiratoria	> a 20 respiraciones por minuto o pCO2 < a 32 mmHg
Recuento de leucocitos	> a 12.000 /mm^3 o < a 4.000 /mm^3

La presencia de 2 o más criterios definen SRIS.

7. Tratamiento

Se pueden distinguir dos fases en el tratamiento de la PA, la primera comprende el tratamiento precoz y la segunda fase (sólo en pancreatitis moderadas a graves) abarca el manejo de las complicaciones locales sintomáticas.

7.1 Tratamiento precoz

Los principales fundamentos del tratamiento precoz son la fluidoterapia, el aporte nutricional, la analgesia y únicamente en algunos casos concretos la antibioterapia y la realización de una colangiopancreatografía retrógrada endoscópica (CPRE).

En la PA con frecuencia se produce un estado de hipovolemia por varios motivos como el secuestro de fluidos, el incremento de pérdidas y la disminución de la ingesta de líquidos. Una hipovolemia grave puede conducir a la hipoperfusión orgánica lo que puede contrarrestarse con una fluidoterapia adecuada. Sin embargo, una hidratación excesiva puede tener efectos adversos como el edema pulmonar y el desarrollo de síndrome compartimental por lo que administrar un volumen de fluidoterapia correcto es de capital importancia [35, 36]. El volumen de fluidoterapia óptimo en PA ha sido objeto de controversia en las últimas décadas. En dos ensayos clínicos aleatorizados que incluyeron pacientes con PA grave la administración de fluidoterapia agresiva se asoció a más morbi-mortalidad, aunque estos ensayos presentaron importantes debilidades metodológicas [37, 38]. En cambio, otro ensayo clínico más reciente pero también con limitaciones metodológicas, mostró benefició de la administración de fluidoterapia agresiva en PA leve [39]. Ensayos clínicos más robustos son necesarios para establecer el volumen exacto de fluidoterapia óptimo. Así, la evidencia de las recomendaciones en este aspecto es débil, recomendando las principales guías en PA una fluidoterapia basada en objetivos [40]. En cuanto al tipo de fluido, la solución de Ringer-Lactato parece disminuir la respuesta inflamatoria en comparación con el suero salino [41].

En las PA leves la reintroducción de la dieta oral precozmente es segura y acorta la estancia hospitalaria. Además, no es necesario comenzar con dieta líquida, se puede comenzar con dieta sólida ya que es bien tolerada [42]. En las PA moderadas-graves, se puede intentar comenzar también con dieta oral, pero si no es tolerada a los 3-4 días será necesario un aporte nutricional enteral por vía nasoyeyunal o nasogástrica [43]. En estos pacientes, la nutrición enteral es claramente superior a la nutrición parenteral en términos de complicaciones infecciosas, FO y mortalidad [44].

Hay una escasez de ensayos clínicos sobre las diferentes pautas de analgesia que impide hacer recomendaciones firmes. Los opiáceos pueden disminuir la necesidad de analgesia suplementaria sin producir efectos adversos [45]. Los antinflamatorios no esteroideos y el metamizol pueden ser utilizados, pero teniendo en cuenta sus efectos adversos; la analgesia epidural puede ser una alternativa en caso de dolor intenso. Por último, la antibioterapia está indicada en caso de infección de la necrosis pancreática o

peripancreática o de otro origen, pero no como profilaxis, y la realización de CPRE está indicada en caso de colangitis aguda [40].

Uno de los objetivos de esta tesis doctoral será realizar una revisión bibliográfica de los aspectos más importantes del tratamiento precoz de la PA.

7.2 Tratamiento necrosis pancreática

El drenaje o desbridamiento de la necrosis pancreática está indicado en pacientes con necrosis infectada o en los casos de necrosis pancreática estéril con clínica relevante secundaria (dolor abdominal y vómitos persistentes, obstrucción de la luz gastrointestinal, obstrucción biliar o SRIS persistente) [46]. En general, el drenaje y/o desbridamiento se debe intentar retrasar hasta las 4 semanas desde el inicio de la PA, tiempo en el cual las colecciones necróticas están organizadas y bien delimitadas [46, 47]. En cuanto a las técnicas empleadas para el drenaje y/o desbridamiento se sigue un esquema escalonado (*step-up approach*) desde las técnicas menos invasivas inicialmente a las técnicas más agresivas posteriormente sólo en el caso de que las primeras fallen. Así, se comienza con un drenaje endoscópico y/o percutáneo, y se procede posteriormente a un desbridamiento endoscópico o una cirugía mínimamente invasiva en caso de que la infección de la necrosis no se controle. Como última opción quedaría la cirugía abierta [47, 48].

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Objetivos de la tesis

Capítulo 1: Determinantes de gravedad en pancreatitis aguda

Como se ha descrito en la introducción, la PA es una enfermedad muy heterogénea con pacientes que evolucionan rápidamente hacia la curación y pacientes que desarrollan complicaciones que prolongan su hospitalización con una morbilidad y mortalidad significativas. Dada esta heterogeneidad se requiere una sólida clasificación de PA para identificar los diferentes subgrupos de pacientes. El primer gran consenso de clasificación de PA que fue ampliamente aceptado fue la Clasificación de Atlanta de 1993 que dividía a los pacientes en dos categorías, leve y grave [1]. La categoría leve era homogénea y albergaba pacientes con similar pronóstico pero la categoría grave era muy heterogénea con pacientes con una morbi-mortalidad muy diferente (desde pacientes simplemente con complicaciones locales pero sin riesgo vital hasta casos con FO asociado a alta mortalidad). En los siguientes 20 años se produjeron avances en el conocimiento de la fisiopatología, historia natural, complicaciones y tratamiento de la PA que se vieron plasmados en dos nuevas clasificaciones, la clasificación basada en determinantes [2] y la clasificación revisada de Atlanta [3] (*Tablas 2 y 3*) publicadas en 2012 y 2013 respectivamente. Estas clasificaciones han sido evaluadas en varios estudios, la mayoría de ellos son retrospectivos o análisis retrospectivos de bases de datos adquiridas de forma prospectiva. Además, la mayoría de los pacientes incluidos en estos análisis provenían sólo de 1 o 2 centros hospitalarios diferentes [4, 5]. El único estudio prospectivo multicéntrico disponible antes de 2019 sólo incluyó pacientes provenientes de Unidades de Cuidados Intensivos (UCI) [6]. Todo ello se asociaba a una muy limitada validez externa de estos estudios. Por ello el objetivo del primer capítulo de esta tesis es realizar un estudio prospectivo a escala nacional diseñado para validar las diferentes clasificaciones de gravedad en PA e investigar qué determinantes de la PA se asocian independientemente a una peor evolución.

Capítulo 2: Influencia de la edad, el índice de masa corporal y la comorbilidad en la evolución clínica de la pancreatitis aguda: un estudio prospectivo multicéntrico a escala nacional.

A lo largo de la historia del conocimiento sobre la PA se ha realizado un esfuerzo en intentar pronosticar qué pacientes tendrán un curso más leve de la enfermedad y cuáles una evolución más tórpida, con una morbi-mortalidad incrementada. Así, los pacientes con pronóstico de gravedad podrían ser monitorizados más atentamente y si desarrollaban FO éste podría ser detectado y tratado más precozmente.

Dentro de los diferentes factores pronósticos, muchos estudios han evaluado las características basales de los pacientes con PA, en concreto la edad, la comorbilidad y la presencia de obesidad. Sin embargo, la mayoría de estos estudios provenían de un único centro hospitalario o tenían un pequeño número de pacientes incluidos o derivaban de bases administrativas, sufriendo así problemas de generabilidad y reproductividad [7, 8]. Además, pocos de estos estudios han incluido a la vez estas tres características basales (la edad, las comorbilidades y el índice de masa corporal) en sus modelos estadísticos multivariantes para poder estudiar su efecto independiente en la evolución de la PA. Por ello, el objetivo del segundo capítulo de esta tesis es evaluar la influencia de la edad, un índice de masa corporal elevado y la comorbilidad en la mortalidad, FO y estancia hospitalaria de los pacientes con PA.

Capítulo 3: Patrones de consumo de grasa en la dieta y curso clínico de la pancreatitis aguda en España.

Estudios experimentales *in vitro* que emplearon células pancreáticas muestran que los ácidos grasos insaturados (UFAs, de sus siglas en inglés *Unsaturated Fatty Acids*) están asociados con inflamación y necrosis celular mientras que los ácidos grasos saturados no son tan dañinos. Estos experimentos sugieren que los UFAs producen necrosis de las células acinares pancreáticas a nivel local y su liberación al torrente circulatorio tiende a producir daño a nivel renal, pulmonar y del endotelio. Los UFAs son los principales ácidos grasos del páncreas y en el curso de la PA por la acción de la enzima lipasa se puede producir su liberación con el consiguiente efecto tóxico a nivel local y sistémico que hemos comentado [9-11]. Por otra parte, el diferente consumo de grasa en la dieta afecta a la composición de grasa corporal y concretamente pancreática. En modelos animales se ha comprobado que dietas ricas en determinados ácidos grasos conllevan cambios en la composición de la grasa corporal murina, adquiriendo mayor proporción

de éstos, es decir, parece que la dieta influye en la proporción de ácidos grasos concretos de la grasa corporal [12, 13]. Consecuentemente se podría plantear que diferentes consumos de tipos de grasa en la dieta pueden producir diferente composición de la grasa pancreática y en el contexto de una PA conducir a una diferente predisposición a toxicidad y por tanto gravedad de la PA. Por ello, el objetivo del tercer capítulo de esta tesis doctoral es comparar el curso clínico de la PA en regiones de España que tienen diferentes patrones de consumo de grasa.

Capítulo 4: Hacia un manejo de la pancreatitis aguda personalizado y basado en la evidencia

El objetivo del cuarto y último capítulo de esta tesis es presentar una revisión de varios aspectos fundamentales en el manejo de la PA. Esta revisión tendrá un enfoque docente, educativo. Se presentará la evidencia científica disponible en cuanto al diagnóstico, etiología, historia natural, clasificaciones y tratamiento precoz de la PA.

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Aportaciones del doctorando

Guillermo García Rayado ha estado implicado intensamente en diferentes proyectos de investigación en enfermedades inflamatorias y neoplásicas pancreáticas, principalmente en el campo de la PA. Estos proyectos han sido liderados por el doctor *Enrique de Madaria Pascual* perteneciente al *Hospital General Universitario de Alicante-Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL)* y por el Profesor *Ángel Lanas Arbeloa*, Catedrático de la Universidad de Zaragoza y Director Científico del *Instituto de Investigación Sanitaria Aragón (IIS Aragón)*. Además, la estancia del doctorando en el prestigioso centro *Johns Hopkins Hospital* en Baltimore (Estados Unidos) ha permitido consolidar conocimientos en el ámbito clínico e investigador. El doctorando ha contribuido de forma esencial en el diseño, desarrollo, análisis y publicación de los diferentes artículos científicos fruto de los proyectos de investigación en PA que conforman esta tesis, y que han sido aceptados en revistas científicas internacionales de reconocido prestigio.

Específicamente, su papel en las siguientes publicaciones ha sido el siguiente:

1.- Sternby H, Bolado F, Canaval-Zuleta HJ, Marra-López C, Hernando-Alonso AI, Del-Val-Antoñana A, García-Rayado G, et al. Determinants of Severity in Acute Pancreatitis: A Nation-wide Multicenter Prospective Cohort Study. Ann Surg. 2019; 270(2):348-355.

Esta publicación es fruto del proyecto *Atlantis* que consistió en un estudio prospectivo multicéntrico en el que participaron 23 hospitales de España, liderado por el doctor *Enrique de Madaria* desde el *Hospital General Universitario de Alicante*. El doctorando fue clave en el desarrollo del estudio, principalmente en la coordinación con los diferentes centros a lo que se sumó la inclusión y recogida de datos de 134 pacientes con PA en su centro hospitalario (*Hospital Clínico Universitario Lozano Blesa*). A continuación, llevó a cabo una revisión-purgado de toda la base de datos multicéntrica que incluyó un total de 1665 episodios de PA, recuperando datos perdidos o incongruentes para optimizar y fortalecer los análisis estadísticos posteriores. Para

conseguir dicho propósito mantuvo un contacto activo con los diferentes centros hospitalarios de los que provenían los pacientes con episodios de PA. Además, el doctorando colaboró en la revisión del manuscrito y en la aprobación de la versión final para su publicación.

2.- Moran RA, García-Rayado G, de la Iglesia-García D, Martínez-Moneo E, Fort-Martorell E, Lauret-Braña E, et al. Influence of age, body mass index and comorbidity on major outcomes in acute pancreatitis, a prospective nation-wide multicentre study. United European Gastroenterol J. 2018; 6(10):1508-1518.*

** Co-primer autor*

El doctorando participó en la concepción y diseño de este segundo análisis de la base de datos prospectiva y multicéntrica de PA *Atlantis*, con el objetivo de estudiar la influencia de la edad, el índice de masa corporal y la comorbilidad en la evolución de la PA. Además, el doctorando contribuyó en el análisis estadístico e interpretación de los datos, en la elaboración de comunicaciones que fueron aceptadas en congresos nacionales e internacionales y en la redacción del manuscrito. Por último, participó en la revisión del manuscrito y en la aprobación final de la versión para ser publicada.

3.- García-Rayado G, Varela-Moreiras G, Lanas Á, Ferrández Á, Balza-Lareu N, Cervera JI, et al. Dietary Fat Patterns and Outcomes in Acute Pancreatitis in Spain. Front Med (Lausanne). 2020; 7:126.

Se trata de un análisis combinando de los datos de la base prospectiva y multicéntrica de PA *Atlantis* y la base nutricional *ANIBES (Anthropometric data, macronutrients and micronutrients intake, practice of physical activity, socioeconomic data, and lifestyles in Spain).* La idea original de este estudio corresponde al doctor *Enrique de Madaria* y contó con la colaboración del Profesor *Gregorio Varela Moreiras*, Presidente de la *Fundación Española de la Nutrición*. El estudio requirió la implicación activa del doctorando en todos los aspectos relacionados con el diseño del estudio, la unificación de los datos, el análisis de los datos, la elaboración de comunicaciones y la redacción del manuscrito.

4.- García-Rayado G, Cárdenas-Jaén K, de-Madaria E. Towards evidence-based and personalised care of acute pancreatitis. United European Gastroenterol J. 2020; 8(4):403-409.

En esta publicación en formato de revisión el doctorando ejerció una posición de líder y fue el principal responsable de la revisión bibliográfica, redacción, revisión y envío del manuscrito.

Capítulos

Capítulo 1: Determinantes de gravedad en pancreatitis aguda

1.1 Metodología

El proyecto *Atlantis* fue auspiciado por la *Asociación Española de Pancreatología (AESPANC)* y la *Asociación Española de Gastroenterología (AEG).* Se llevó a cabo a través de un estudio prospectivo en el que pacientes mayores de 18 años con PA fueron incluidos consecutivamente en 23 hospitales españoles. De los centros participantes, 20 (87%) fueron de tercer nivel y 3 (13%) fueron de segundo nivel. Para el diagnóstico de PA se requirió la presencia de al menos dos de los siguientes criterios [1]: A) dolor abdominal típico, B) incremento de amilasa y/o lipasa sérica mayor de 3 veces el límite superior de la normalidad y/o C) imagen compatible en las pruebas de imagen. Los pacientes con pancreatitis crónica fueron excluidos. En cada centro hospitalario participaron en el estudio 1 o 2 gastroenterólogos o cirujanos generales y 1 radiólogo. La presencia de complicaciones locales se evaluó con la realización de un TAC. De acuerdo con la práctica clínica a los pacientes con curso leve de la enfermedad no se les realizó TAC y se asumió que estos pacientes no tenían complicaciones locales.

Las variables de resultado *(outcomes)* fueron: días desde el ingreso hasta la reintroducción efectiva de la dieta oral, necesidad de tratamiento invasivo, ingreso en UCI, estancia hospitalaria y mortalidad hospitalaria. Dentro de la variable tratamiento invasivo se incluyeron los procedimientos invasivos para el tratamiento de la PA, pero no procedimientos para problemas colaterales como la coledocolitiasis, colangitis, colecistitis aguda, etc. En el análisis estadístico, para estudiar la asociación de los posibles determinantes de gravedad con las variables de resultado se realizó en primer lugar un análisis univariante y a continuación un análisis multivariante que incluyó la edad, la comorbilidad definida según el Índice de Comorbilidad de Charlson [2], el sexo, la etiología alcohólica y la PA recurrente. Detalles adicionales sobre el análisis estadístico se incluyen en la versión original del manuscrito que se adjunta a continuación.

1.2 Resultados

En total se incluyeron 1655 pacientes con PA. La edad media de los pacientes fue de 66 años, 891 (53.8%) fueron varones y la comorbilidad fue frecuente. La etiología de la PA más frecuente fue la biliar seguida de la alcohólica. 234 (14.1%) pacientes desarrollaron FO y en 113 (6.8%) pacientes el FO fue persistente. En 444 (26.8%) pacientes se produjeron complicaciones locales y 70 pacientes (4.2%) fallecieron.

En cuanto a la validación y comparación de las clasificaciones de gravedad, la Clasificación de Atlanta (AC) tuvo una curva ROC (*receiver operating characteristic curve*) significativamente menor que la clasificación basada en determinantes (DBC) y que la clasificación revisada de Atlanta (RAC) en cuanto a la mortalidad de la PA. Además, la AC tuvo una tendencia no significativa a una menor curva ROC en comparación con la RAC en cuanto a ingreso en UCI, y una curva ROC significativamente menor en comparación con la DBC en cuanto a ingreso en UCI y necesidad de tratamiento invasivo. No hubo diferencias significativas entre la RAC y la DBC.

En lo referente a los determinantes de gravedad, el FO transitorio y el FO persistente se asociaron a una mayor morbilidad y mortalidad en comparación con los pacientes sin FO. El FO persistente se asoció a una mortalidad mucho mayor (aOR de 16) comparado con el FO transitorio. Todas las complicaciones locales (incluidas las colecciones agudas no necróticas) se asociaron independientemente a mayor morbi-mortalidad. Sin embargo, si en el análisis multivariante se incluye el FO persistente, las complicaciones locales pierden su asociación significativa con la mortalidad. Por otra parte, todas las complicaciones locales fueron asociadas a mayor riesgo de desarrollar FO persistente, pero sobre todo la combinación de necrosis pancreática y necrosis peripancreática (aOR 35.7). La infección de la necrosis pancreática se asoció a mayor morbilidad y mortalidad en comparación con la necrosis estéril, pero si en el análisis multivariante se incluye el FO persistente pierde la asociación significativa con la mortalidad. Por último, el fallo multiorgánico se relacionó con mayor morbi-mortalidad en comparación con el FO simple.

Determinants of Severity in Acute Pancreatitis

A Nation-wide Multicenter Prospective Cohort Study

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Objective: The aim of this study was to compare and validate the different classifications of severity in acute pancreatitis (AP) and to investigate which characteristics of the disease are associated with worse outcomes.

Summary of Background Data: AP is a heterogeneous disease, ranging from uneventful cases to patients with considerable morbidity and high mortality rates. Severity classifications based on legitimate determinants of severity are important to correctly describe the course of disease.

Methods: A prospective multicenter cohort study involving patients with AP from 23 hospitals in Spain. The Atlanta Classification (AC), Revised Atlanta Classification (RAC), and Determinant-based Classification (DBC) were compared. Binary logistic multivariate analysis was performed to investigate independent determinants of severity.

Results: A total of 1655 patients were included; 70 patients (4.2%) died. RAC and DBC were equally superior to AC for describing the clinical course of AP. Although any kind of organ failure was associated with increased morbidity and mortality, persistent organ failure (POF) was the most significant determinant of severity. All local complications were associated with worse outcomes. Infected pancreatic necrosis correlated with high morbidity, but in the presence of POF, it was not associated to higher mortality when compared with sterile necrotizing pancreatitis. Exacerbation of previous comorbidity was associated with increased morbidity and mortality.

Conclusion: The RAC and DBC both signify an advance in the description and differentiation of AP patients. Herein, we describe the complications of the disease independently associated to morbidity and mortality. Our findings are valuable not only when designing future studies on AP but also for the improvement of current classifications.

Keywords: acute pancreatitis, Atlanta classification, determinant-based classification, follow-up study, infection, local complications, morbidity, mortality, necrosis, organ failure, revised Atlanta classification, revision of the Atlanta classification, severity

(*Ann Surg* 2018;xx:xxx–xxx)

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This study received no funding.

The authors have no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

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ISSN: 0003-4932/16/XXXX-0001

DOI: 10.1097/SLA.0000000000002766

The incidence of acute pancreatitis (AP) is rising globally, implying a significant burden on health care systems.[1,2] Although approximately two-thirds of the AP patients have an uneventful course of disease, the remainder third suffer considerable morbidity and an increased risk of death.[3] Given this heterogeneity, a solid severity classification is needed to identify different subsets of patients. An appropriate stratification method demands unified definitions and terminologies to obtain good internal and external validity. Several attempts have emerged[4–7], but it was not until the International Symposium in Atlanta 1992 that a system was widely adopted.[8] The Atlanta classification (AC) provided descriptive terms for local and systemic complications as well as a dichotomous stratification into mild and severe disease. However, after 20 years, substantial progress has been made in the understanding of pathophysiological pathways, disease-related complications, imaging, and treatment of AP.[9–14] Thus, in 2012, 2 new classifications were introduced: The Revision of the Atlanta Classification (RAC) and the Determinant-Based Classification (DBC).[15,16] The RAC provides definitions for diagnostic criteria for AP, local complications (including detailed radiological definitions), systemic complications, the description of an early and late phase, and a 3-category severity classification.[15]

The DBC was based on factors that are causally associated with severity of AP, that is, local and systemic ''determinants.''[16] The DBC provides a 4-category severity classification.

The severity categories of the AC, the RAC, and the DBC are outlined in Table 1. Since their publication, the latter 2 classifications have been studied in various settings. Most studies were purely retrospective or retrospective analysis of prospective databases as well as a majority of these works analyzed results from just 1 or 2 centers.[3,17–30] The only purely prospective multicenter study was focused solely on patients admitted to the intensive care unit (ICU), thus involving only severe cases.[31] Furthermore, most of the above-mentioned studies came from referral centers. These properties compromise the external validity of available data regarding the assessment of the severity classifications on AP. Some assumptions or discrepancies of the new classifications needed external validation, for example, the role of acute peripancreatic fluid collections (APFCs), which are not mentioned in any category of the DBC; the role of infected pancreatic necrosis (IPN), which is not part of any category in the RAC, early versus late OF (which are not particularly addressed in any of them), single versus multiple OF, etc.

We aimed to perform a nation-wide prospective study specifically designed to validate the different classifications of severity and to investigate which independent characteristics of the disease are associated with worst outcomes.

METHODS

Design

The Atlantis project, a nation-wide prospective cohort study, was created under the auspices of the Spanish Association of Pancreatology (AESPANC) and the Spanish Association of Gastroenterology (AEG) to validate and compare the determinants of severity and the severity classifications as well as to ascertain the role of comorbidity in the course of AP. The latter aim is not addressed in this article. The study followed the ethical standards of the Helsinki Declaration of 2013 and was approved by the local ethical committee at each center. To enter the study, a signed informed consent was required from the patient or a relative.

Patients

Adult (≥18 years of age) patients with AP were prospectively and consecutively enrolled at 23 Spanish centers from June 2013 to February 2015. Among the centers, 20 (87%) were third-level hospitals and 3 (13%) were second-level hospitals. For the diagnosis of AP, presence of at least 2 of the following criteria were required: (1) typical upper abdominal pain, (2) increase in serum amylase and/or lipase above 3 times the upper limit of normal, and (3) imaging compatible with AP.[15] Patients with chronic pancreatitis (calcifications and/or dilated main pancreatic duct) were excluded. Each center had 1 to 2 gastroenterologists or surgeons responsible for patient recruitment and the acquirement of data. The morphological characteristics of the disease, as seen on computed tomography (CT) scan, were described by a local radiologist at each center.[15] All radiologists were blinded for clinical outcomes. CT scan was not performed on all patients with a mild course of disease (short-lasting pain, absence of clinical and biochemical markers of systemic inflammatory response, and quick recovery including rapid oral refeeding). In data analysis, we assumed that these patients did not have local complications.

Outcome Variables

Outcome variables were the following: days from admission to successful oral refeeding, need for invasive treatment, ICU admission, length of hospital stay, and in-hospital mortality. Need for invasive treatment included invasive procedures aimed to treat direct consequences of pancreatic inflammation or infection of pancreatic collections, such as thoracentesis, endoscopic stenting of disrupted Wirsung duct, endoscopic drainage/necrosectomy, percutaneous drainage, and/or surgery. The invasive treatment of collateral problems, such as choledocholitiasis, cholangitis due to biliary stones, acute cholecystitis, etc, was not included in this

TABLE 1. Definitions of Severity: Atlanta Classification, Revised Atlanta Classification, and Determinant-Based Classification

Classification	Mild	Moderate/ Moderately Severe	Severe	Critical
Atlanta Classification	No OF and no local complications	N/A	OF and/or local complications (necrosis, abscess, and/or pseudocyst)	N/A
Revised Atlanta Classification	No OF, no local nor systemic complications	OF that resolves within 48 h (transient OF) and/or local or systemic complications without persistent OF	Persistent OF (>48 h)	N/A
Determinant-Based Classification	No (peri)pancreatic necrosis and no OF	Sterile (peri)pancreatic necrosis and/or transient (<48 h) OF	IPN or persistent (≥48 h) OF	IPN and persistent (≥48 h) OF

IPN indicates infected (peri)pancreatic necrosis; N/A, not applicable; OF, organ failure; (Peri)pancreatic necrosis, necrosis of the pancreas and/or peripancreatic tissue.

outcome variable. Time to oral refeeding and length of hospital stay were dichotomized using a cut-off of >3.5 and >11.5 days, both which equals to the third quartile (Q3) of the variables in our cohort. We followed the STROBE statement for the reporting of data.[32]

Statistical Analysis

Continuous data were evaluated for normality by the Shapiro-Wilk test and were summarized using mean and standard deviation (SD) or median and interquartile range (IQR) depending on the variable distribution. Qualitative variables were expressed as n (%). The trend for worse outcomes in increasingly severe categories was assessed by means of the Linear-by-Linear Association test when dichotomous, and with the Jonckheere-Terpstra test in case of quantitative variables. The different classifications were compared by means of the area under the receiver operator characteristics curve (AUC). Statistical significance between the different AUCs were determined with the Hanley and McNeil method.[33] Alpha level was 0.05, and the Bonferroni correction was used for multiple comparisons (ie, when comparing AUCs between the 3 classifications, according to the Bonferroni correction, the *P* level of significance decreases to 0.017).

The association of several possible determinants of severity was investigated by means of binary logistic regression analysis, both univariate (odds ratio, OR) and multivariate analysis (adjusted OR, aOR). The model used for multivariate analysis included age and comorbidity by means of the Charlson Comorbidity Index (cutoff ≥3), sex, alcoholic etiology, and recurrent AP (≥1 previous episode).[34]

All statistical calculations were performed with SPSS 20.0 (SPSS Inc., Armonk, NY).

RESULTS

Basal Characteristics and Outcomes

In total, 1655 patients were included. The median (IQR) number of patients per center was 73 (IQR: 52 to 87). Baseline patient characteristics and outcomes are presented in Table 2. Median age was 66 years; sex distribution was almost equal between males and females and comorbidity was frequent. The patients tended to be overweight and gallstones was the most frequent etiology. Hypertriglyceridemic AP was infrequent (26 cases, 1.6%) and was not associated with worse course of disease (data not showed). Among the 234 (14.1%) patients who developed OF, 113 cases (48.3% among the patients with OF) lasted for more than 48 hours (persistent OF; POF). Detailed frequency of the subtypes of POF is summarized in Table 2 as well as data regarding the other investigated outcomes. Local complications were described in 444 cases (26.8%) (Table 2). Seventy patients (4.2%) died; for 21 patients (30%), death was caused by sterile OF and 17 (24.3%) patients died from septic OF due to IPN, whereas sepsis not related to IPN was the cause of death in 10 (14.3%) cases. The remaining patients died due to exacerbation of previous comorbidity (6 cases; 8.6%) and other causes (16 patients; 22.9%).

TABLE 2. Basal Characteristics and Outcomes

Characteristics and Outcomes	Overall
N	1655
Age, median (IQR), y	66 (51–79)
Male sex, n (%)	891 (53.8%)
BMI, median (IQR), kg/m^2	26.8 (24.3–29.7)
CCI, median (IQR) points	3 (1–5)
AP episode, n (%)	
First	1233 (74.5%)
Second	273 (16.5%)
Third or more	149 (9%)
Transferred from another center, n (%)	105 (6.3%)
Etiology, n (%)	
Gallstones	984 (59.5%)
Alcohol	251 (15.2%)
Idiopathic	235 (14.2%)
Other	185 (11.2%)
Organ failure, n (%)	
Transient OF (≤48 h)	121 (7.3%)
Overall POF (>48 h)	113 (6.8%)
Early (first week) POF	89 (5.4%)
Late (>7th day) POF	24 (1.5%)
Single organ failure	141 (8.5%)
Multiple organ failure	93 (5.6%)
Sterile POF	76 (4.6%)
Septic POF (infected necrosis)	37 (2.2%)
Local complications *, n (%)	
No local complications	1211 (73.2%)
APFC	163 (9.8%)
Peri(pancreatic) necrosis	281 (17%)
Isolated pancreatic necrosis	73 (4.4%)
Isolated peripancreatic necrosis	75 (4.5%)
Pancreatic and peripancreatic necrosis	133 (8%)
Infected peri(pancreatic) necrosis	59 (3.6%)
Need for invasive treatment, n (%)	87 (5.3%)
Time to oral refeeding, median (IQR), d	2 (1.1–3.5)
ICU admission, n (%)	126 (7.6%)
Hospital stay, median (IQR)	7 (4.6–11.5)
Mortality, n (%)	70 (4.2%)

AP indicates acute pancreatitis; APFC, acute peripancreatic fluid collections; BMI, body mass index; CCI, Charlson comorbidity index; ICU, intensive care unit; IQR, interquartile range (Q1-Q3); OF, organ failure; Peri (pancreatic) necrosis, pancreatic and/or peripancreatic necrosis; POF, persistent organ failure.

*Patients with a mild course of disease did not undergo a CT scan for ethic reasons (futile exposure to radiation) and were assumed as not having local complications.

Validation and Comparison of the Severity Classifications

Increasing severity categories were associated to increasingly worse outcomes in all 3 classifications (Table 3). The AUCs of the individual classifications for the different outcome variables are shown in supplementary Table 1, http://links.lww.com/SLA/B407. The AC had a trend toward a lower AUC for ICU admission than the RAC and a statistically significant lower AUC for the need for ICU admission and invasive treatment than the DBC. Finally, the AC had a statistically significant lower AUC than the RAC and DBC regarding mortality. There were no significant differences between the RAC and DBC.

Determinants of Morbidity and Mortality

Effect of the Duration of OF on Outcomes

Compared with patients without organ failure, transient OF and POF were both associated with increased morbidity and mortality (Table 4), where POF had greater morbidity than transient OF. When excluding patients without OF, POF had an aOR of 16 (7.2 to 35.5) for mortality compared with transient OF.

Local Complications and Outcomes

Compared with not having local complications, APFC as well as the various groups with necrosis were independently associated with increased morbidity and mortality (Table 5).

Local complications were not associated with mortality if POF was added to the model (data not shown). Hence, the relationship between POF and local complications was additionally studied (Supplementary Table 2, http://links.lww.com/SLA/B407).

TABLE 3. Outcomes According to the Different Severity Classifications

Classification	Severity Category	Time to Oral Refeeding Median (IQR), d	Need for Invasive Treatment n (%)	Intensive Care Unit Admission n (%)	Hospital Stay Median (IQR), d	Mortality n (%)
Atlanta	Mild n = 1175	1.6 (1–2.8)	3 (0.3%)	2 (0.2%)	6.2 (4.1–8.7)	1 (0.1%)
	Severe n = 480	3.4 (1.6–9.7)	84 (17.5%)	124 (25.8%)	13.8 (7.9–25.5)	69 (14.4%)
	P	<0.001	<0.001	<0.001	<0.001	<0.001
Revision of Atlanta	Mild n = 1076	1.6 (0.9–2.6)	2 (0.2%)	1 (0.1%)	5.9 (4–8.2)	1 (0.1%)
	Moderately severe n = 466	2.9 (1.5–6.1)	31 (6.7%)	43 (9.2%)	11.4 (7.4–18.3)	10 (2.1%)
	Severe n = 113	10.6 (3.3–27.5)	54 (47.8%)	82 (72.6%)	39.1 (16.4–69.9)	59 (52.2%)
	P	<0.001	<0.001	<0.001	<0.001	<0.001
Determinant-based	Mild n = 1247	1.6 (1–2.8)	4 (0.3%)	3 (0.2%)	6.3 (4.2–9.1)	1 (0.1%)
	Moderate n = 274	3.1 (1.6–7.1)	8 (2.9%)	35 (12.8%)	12.9 (7.6–19.2)	11 (4%)
	Severe n = 97	9.4 (3.4–26.2)	38 (39.2%)	52 (53.6%)	34.3 (16.5–66)	38 (39.2%)
	Critical n = 37	24.2 (10.1–67.2)	37 (100%)	36 (97.3%)	88 (54.4–119.7)	20 (54.1%)
	P	<0.001	<0.001	<0.001	<0.001	<0.001

P: statistical significance according to the Linear-by-Linear Association test (dichotomous outcome variables) or Jonckheere-Terpstra test (quantitative outcome variables). IQR indicates interquartile range.

Compared with not having local complications, APFC, isolated peripancreatic or pancreatic necrosis as well as combined peri(-pancreatic) necrosis were all independently associated with increased risk of POF. Combined pancreatic and peripancreatic necrosis had a stronger association to POF than the other local complications (aOR 35.7).

Effect of IPN

IPN was associated with a higher aOR than sterile peri (pancreatic) necrosis regarding time to oral refeeding > Q3, need for invasive treatment, ICU admission, hospital stay >Q3, and mortality [reference category: patients without peri (pancreatic) necrosis, Table 6]. In addition, POF was more frequent in IPN (62.7%) than in sterile necrosis (16.2%), $P < 0.001$. When POF was added as a covariate in multivariate analysis (Table 6), IPN was anew associated with higher aOR (CI 95%) than sterile peri (pancreatic) necrosis regarding time to oral refeeding >Q3, invasive treatment and hospital stay >Q3. However, in this latter model, mortality was similar between infected and noninfected peri (pancreatic) necrosis. POF with concurrent IPN correlated to a higher aOR for time to oral refeeding >Q3 and need for ICU admission compared with sterile POF (Supplementary Table 3, http://links.lww.com/SLA/B407).

Association Between Early (Within the First Week) versus Late (>First Week) POF and Outcomes

Late POF was associated with a higher need for invasive treatment than early POF (Supplementary Table 4, http://links.lww.com/SLA/B407). If IPN was added to the model, no independent association was found between late OF and need for invasive treatment, [aOR 1 (0.1 to 7)].

Single Organ Failure Versus Multiple Organ Failure: Effect on Outcomes

Multiple organ failure was independently associated with higher morbidity and mortality than single organ failure (Supplementary Table 5, http://links.lww.com/SLA/B407).

TABLE 4. Association Between Duration of Organ Failure and Outcomes

		Time to Oral Refeeding*	Need for Invasive Treatment	Intensive Care Unit Admission	Hospital Stay*	Mortality
No OF (n = 1421)	n (%) or median (IQR)	1.8 (1–3.1)	28 (2%)	14 (1%)	6.6 (4.4–10.2)	2 (0.1%)
	OR	1	1	1	1	1
	aOR	1	1	1	1	1
Transient OF (n = 121)	n (%) or median (IQR)	3.3 (1.6–7.5)	5 (4.1%)	30(24.8%)	13.3 (7.1–23.1)	9 (7.4%)
	OR	3.3 (2.2–4.9)	2.1 (0.8–5.7)	33 (17–64.7)	5.1 (3.4–7.6)	57 (12.2–267)
	aOR	3.3 (2.2–5)	2.7 (1–7.2)	57.1 (26.7–122.2)	4.7 (3.1–7)	47.5 (10.1–224)
POF (n = 113)	n (%) or median (IQR)	10.6 (3–27.5)	54 (47.8%)	82 (72.6%)	39.1 (16.4–70)	59 (52.2%)
	OR	12 (6.8–21.8)	45.5 (27–77)	266 (136–519)	25 (11.2–57)	775 (185–3256)
	aOR	12.6 (7–22.6)	64.9 (35.8–117.8)	623 (269–1444)	25.2 (11.2–56.5)	767 (181–3251)

Multivariate analysis includes sex, comorbidity and age by means of the Charlson Comorbidity Index (cutoff ≥3), recurrent AP (≥1 previous episode), and alcoholic etiology. aOR indicates adjusted odds ratio; IQR, interquartile range (Q1-Q3); OF, organ failure; OR, odds ratio; POF, persistent organ failure.

*OR and aOR of the variables ''time to oral refeeding'' and ''hospital stay'' are given for starting effective oral refeeding >3.5 days (Q3) from presentation and having a hospital stay >11.5 days (Q3).

TABLE 5. Local Complications and Outcomes

		Time to Oral Refeeding*	Need for Invasive Treatment	Intensive Care Unit Admission	Hospital Stay*	Mortality
No local complications (n = 1211)	n (%) or median (IQR)	1.6 (1–2.8)	1 (0.1%)	20 (1.6%)	6.1 (4.1–8.9)	23 (1.9%)
	OR	1	1	1	1	1
	aOR	1	1	1	1	1
APFC (n = 163)	n (%) or median (IQR)	2.5 (1.4–4.4)	6 (3.7%)	13 (8%)	9.5 (6.8–14.7)	7 (4.3%)
	OR	2.6 (1.8–3.8)	46 (6–387)	5.2 (2.5–10.6)	3.3 (2.3–4.8)	2.3 (1–5.5)
	aOR	2.7 (1.8–3.9)	49 (6–411)	5.2 (2.5–10.7)	3.8 (2.6–5.5)	2.9 (1.2–6.9)
Isolated peripancreatic fat necrosis (n = 75)	n (%) or median (IQR)	4.4 (1.9–13.2)	8 (10.7%)	12 (16%)	13.3 (8.7–24)	7 (9.3%)
	OR	7.7 (4.6–12.8)	144 (18–1172)	11.3 (5.3–24.2)	8.5 (5.1–14.2)	5.3 (2.2–12.8)
	aOR	8.1 (4.8–13.6)	147 (18–1199)	11.5 (5.4–24.8)	10.1 (5.9–17.1)	6.9 (2.8–17.2)
Isolated parenchymal necrosis (n = 73)	n (%) or median (IQR)	3.3 (1.7–10.3)	10 (13.7%)	18 (24.7%)	13.6 (8–20.5)	7 (9.6%)
	OR	4 (2.4–6.8)	192 (24–1524)	19.5 (9.8–38.9)	6.9 (4.1–11.5)	5.5 (2.3–13.2)
	aOR	4.2 (2.4–7.1)	212 (26–1692)	20 (9.9–40.7)	7.9 (4.6–13.5)	7.3 (2.9–18.1)
Pancreatic and peripancreatic necrosis (n = 133)	n (%) or median (IQR)	8 (2.5–23.5)	62 (46.6%)	63 (47.4%)	26 (14.2–59.2)	26 (19.5%)
	OR	11.6 (7.4–18)	1057 (144–7731)	53.6 (31–93.6)	24.4 (14.6–40.73)	12.6 (6.9–22.8)
	aOR	12 (7.5–18.7)	1143 (155–8430)	53.2 (30.1–94)	29.7 (17.4–50.6)	16.8 (8.9–31.5)

Multivariate analysis includes sex, comorbidity and age by means of the Charlson Comorbidity Index (cutoff ≥3), recurrent AP (≥1 previous episode), and alcoholic etiology.
aOR indicates adjusted odds ratio; APFC, acute peripancreatic fluid collections; IQR, interquartile range; OF, organ failure; OR, odds ratio; Peri (pancreatic) necrosis, pancreatic and/or peripancreatic necrosis; POF, persistent organ failure.
*OR and aOR of the variables ''time to oral refeeding'' and ''hospital stay'' are given for starting effective oral refeeding >3.5 days (Q3) from presentation and having a hospital stay >11.5 days (Q3).

TABLE 6. Effect of Sterile and Infected Necrosis on Outcomes

		Time to Oral Refeeding*	Need for Invasive Treatment	Intensive Care Unit Admission	Hospital Stay*	Mortality
No peri (pancreatic) necrosis (n = 1374)	n (%) or median (IQR)	1.7 (1–3.1)	7 (0.5%)	33 (2.4%)	6.4 (4.3–9.6)	30 (2.2%)
	OR	1	1	1	1	1
	aOR†	1	1	1	1	1
	aOR‡	1	1	1	1	1
Sterile peri (pancreatic) necrosis (n = 222)	n (%) or median (IQR)	3.7 (1.9–11.5)	22 (9.9%)	51 (23%)	14.7 (8.5–25.5)	20 (9%)
	OR	5.1 (3.7–6.9)	21.5 (9.1–50.9)	12.1 (7.6–19.3)	7.7 (5.6–10.6)	4.4 (2.5–8)
	aOR†	5.1 (3.7–7)	20.9 (8.6–50.7)	11.6 (7.2–18.8)	8.4 (6–11.8)	5.6 (3.1–10.3)
	aOR‡	4.4 (3.2–6.2)	8.9 (3.4–23)	7.5 (4.2–13.5)	7.4 (5.3–10.4)	1.7 (0.7–4)
Infected peri (pancreatic) necrosis (n = 59)	n (%) or median (IQR)	23.9 (9.9–58)	58 (98.3%)	42 (71.2%)	66.3 (43.5–98.4)	20 (33.9%)
	OR	54 (16.6–178)	11327 (1371–93,583)	100 (52–194.4)	180.5 (24.7–1321.6)	23 (12–44)
	aOR†	54.7 (16.6–179.9)	12729 (15,003–107,791)	99.9 (51–195.4)	213 (29–1569)	31.2 (15.4–63.4)
	aOR‡	30 (8.8–102.1)	7217.7 (815–63,851)	28.4 (11.5–70.1)	134.7 (18–1005.3)	1.9 (0.7–4.8)

aOR indicates adjusted odds ratio; IQR, interquartile range; OR, odds ratio; Peri (pancreatic) necrosis, pancreatic and/or peripancreatic necrosis.
*OR and aOR of the variables ''time to oral refeeding'' and ''hospital stay'' are given for starting effective oral refeeding >3.5 days (Q3) from presentation and having a hospital stay >11.5 days (Q3).
Multivariate analysis: aOR† includes sex, comorbidity and age by means of the Charlson Comorbidity Index (cutoff ≥3), recurrent AP (≥1 previous episode), and alcoholic etiology. aOR‡ includes the variables listed in aOR† as well as persistent organ failure.

Exacerbation of Previous Comorbidity

In the absence of POF, exacerbation of previous comorbidity correlates to increased morbidity and mortality (Supplementary Table 6, http://links.lww.com/SLA/B407).

DISCUSSION

An applicable classification is based on current knowledge regarding the characteristics associated with the course of disease. Correct stratification of disease severity is required for comparison of inter-institutional data, as well as for the development of management strategies and research. This project aimed to be the first multicenter nation-wide prospective study specifically designed to validate the new classifications of severity in AP and investigate which characteristics of the disease are associated with worse outcomes.

As described in previous validation studies on AP classifications, both the RAC and DBC were superior to the AC in stratifying the patients into homogeneous groups.[3,17–30] There were no significant differences between the RAC and DBC.

Regarding determinants of severity, we show that POF is a significant and decisive marker of both morbidity and mortality and therefore should be part of any classification of AP. Our conclusions are in line with findings from previous studies.[35,36] In addition, we showed that all local complications are associated with worse outcomes, particularly combined parenchymal and peripancreatic necrosis. Cell death by necrosis is associated with a sterile inflammatory reaction through the recognition of damage-associated molecular patterns by Toll-like receptors, nucleotide oligomerization domain-like receptors, and other pattern-recognition receptors present in cells of innate immunity.[37] Any local complication is associated with increased cellular and tissue damage when compared with edematous AP, so a higher inflammatory response and increased risk of sterile POF should be expected. Furthermore, local complications may become infected, increasing the risk for septic POF. Regardless, in some cases, a reverse causation bias may associate POF and local complications, for example, aggressive fluid resuscitation may increase the possibility of fluid collections.[38] These results support the RAC, in which patients with any type of local complication but without POF are classified as moderately severe.[15] The DBC only considers necrotizing pancreatitis to be a determinant of severity; however, according to our data, APFC was also independently associated to worse outcomes.[16]

A major question regarding the determinants of severity in AP is the role of IPN. A meta-analysis from the Auckland group comprising almost 1500 patients showed that co-occurring OF and IPN resulted in higher mortality than sterile OF.[39] On the basis of this study, the DBC differentiates patients suffering from both POF and IPN into the most severe (critical) category of AP, whereas the RAC does not take into account the presence of this combination in severity stratification. Our results initially demonstrated that IPN is associated with increased morbidity and mortality compared with sterile peri(pancreatic) necrosis. However, when POF was added to the multivariate analysis, presence of infection was associated to increased morbidity but not mortality. Also, among patients with POF, the mortality was similar in sterile necrosis and IPN: 51.3% and 54.1%, respectively. As IPN implies invasive treatment and prolonged hospital stay, this situation is important per se regarding morbidity.[40] However, its effect on mortality depends on the development of POF, which is more frequent in infected than in sterile necrosis.[40,41] Coincident POF and IPN was, in our data, associated with increased time to oral refeeding and need for ICU admission compared with sterile POF. IPN frequently correlates with late POF, but with infection added to the model, the distinction between early and late POF dissipates. Multiorgan failure was independently associated with increased morbidity and mortality when compared with single organ failure and should be considered in future classifications. Finally, we addressed exacerbation of previous comorbidity. The concept was introduced by the RAC, although not apparently based on published data. In this work, we demonstrate that exacerbation of comorbidities in the absence of POF is certainly associated with worse outcomes, including mortality. A simplified summary of our findings is summarized in Table 7. In accordance with our findings, we suggest taking into consideration the following proposal in future efforts to improve the current classifications of severity:

(1) A mild category involving AP without complications. These are patients with very little morbidity and no mortality, with an excellent course of disease.
(2) A moderate category (increased morbidity), which can be subdivided into 2 subcategories:
   a) Moderate category with low morbidity: including patients with transient organ failure, exacerbation of previous comorbidity, APFCs, or isolated pancreatic or peripancreatic necrosis. These complications are associated with increased morbidity compared with patients in the mild category.
   b) Moderate category with high morbidity, defined by the presence of combined peripancreatic and parenchymal necrosis and/or IPN. These patients have the highest degree of morbidity, including higher time to oral refeeding, higher need for invasive treatment, and higher hospital stay than patients classified as a). Mortality is low in both moderate subcategories.
(3) A severe category: persistent and/or multiple organ failure. These patients have a high risk of death (50%) and also a very

TABLE 7. Summary

	Increased Morbidity	Maximum Morbidity	Increased Mortality	Maximum Mortality
Organ failure and exacerbation of previous comorbidity	Any organ failure Exacerbation of previous comorbidity	POF Multiple organ failure	Any organ failure Exacerbation of previous comorbidity	POF Multiple organ failure
Local complications	All of them	Combined peripancreatic and parenchymal necrosis	Only if POF present	Only if POF present
		IPN	All of them associated with POF	Combined peripancreatic-parenchymal necrosis and IPN highly associated with POF

IPN indicates infected (peri)pancreatic necrosis; POF, persistent organ failure.

aggressive course of disease in terms of morbidity. Multiple organ failure should be included in this category, as those patients have the same probability of death as those with persistent organ failure.

Strengths of this study is its multicenter setting involving a large number of unselected patients. Previous studies have principally involved cohorts from a few centers highly focused on pancreatology, implicating selected data. In addition, our set-up was prospective and specifically designed to validate and compare the severity classifications as well as to investigate the determinants of severity. All these properties contribute to increased external validity. However, this work also has limitations. As there was no central review of CT scans, imaging assessment relied on local radiologists. Hence, morphological categories such as APFC or peri(pancreatic) fat necrosis may be diversely interpreted depending on the center. It is, however, our opinion that these circumstances reflect the routine clinical situation. In addition, as current guidelines regarding radiation exposure were followed, 802 patients (48.5%) patients with a mild course of disease did not undergo a CT scan. Consequently, there might have been undetected local complications. A majority of the recruiters were gastroenterologists, thus some patients admitted to other departments could have gone unnoticed and therefore be lost for recruitment. However, most patients with AP in Spain are treated by gastroenterologists and the small number of possibly undetected patients in this study could not be considered a selection bias. Finally, no formal sample size calculation was made before the study, but the number of patients recruited was higher than in previous studies addressing similar aims.

In conclusion, our findings confirm the superiority of the RAC and DBC in describing different groups of AP patients compared with the AC. POF and multiple organ failure are major determinant of severity in AP and any kind of local complication corresponds to worse outcomes. Presence of IPN implies more severe disease, although it is not associated with higher mortality than sterile necrotizing pancreatitis if POF is present. Exacerbation of previous comorbidity, in the absence of POF, is associated with a rise in both morbidity and mortality. Our study provides data that could be relevant for the design of future severity classifications.

ACKNOWLEDGMENT

The authors wish to thank the Spanish Association of Gastroenterology (AEG) and the Spanish Association of Pancreatology (AESPANC) for their support.

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Capítulo 2: Influencia de la edad, el índice de masa corporal y la comorbilidad en la evolución clínica de la pancreatitis aguda: un estudio prospectivo multicéntrico a escala nacional.

2.1 Metodología

Se trata de un segundo estudio derivado del proyecto prospectivo *Atlantis* que, como se ha comentado en el apartado anterior, incluyó 1655 pacientes con PA. Las principales características de este proyecto han sido explicadas en el apartado 1.1. Para este segundo análisis, la comorbilidad se definió según el Índice de Comorbilidad de Charlson [2] sin incluir la edad en el score. La obesidad fue definida por un índice de masa corporal (IMC) mayor o igual a 30 Kg/m^2 y el sobrepeso por un IMC entre 25 y 30 Kg/m^2. Cada radiólogo describió las complicaciones locales según las definiciones de la RAC. En la variable tratamiento invasivo se incluyeron la necrosectomía abierta quirúrgica, el drenaje y/o necrosectomía endoscópica y el drenaje percutáneo.

En el análisis estadístico, para evaluar los factores asociados a la mortalidad a los 30 días y al FO persistente se utilizó un análisis multivariante proporcional de regresión de Cox. En este análisis multivariante se incluyeron la edad, la comorbilidad, el índice de masa corporal, la PA recurrente, la necrosis pancreática, la necrosis peripancreática, la infección de la necrosis pancreática y la cirugía dentro de los 30 primeros días. En el modelo para la mortalidad la presencia de FO no fue incluida puesto que es una variable intermedia para la mortalidad en PA por lo que su inclusión resultaría en un sesgo de sobreajuste. Para evaluar los factores asociados a una estancia hospitalaria prolongada se utilizó un análisis multivariante de regresión logística que incluyó la edad, la comorbilidad, el índice de masa corporal, la necrosis pancreática, la necrosis peripancreática, el FO transitorio y persistente, la necesidad de tratamiento invasivo y la mortalidad.

2.2 Resultados

En total se incluyeron 1655 pacientes con PA, las principales características basales de estos pacientes se han descrito en el apartado 1.2. En 113 (6.8%) pacientes el FO fue persistente y 70 pacientes (4.2%) fallecieron. De estos 70 pacientes que fallecieron, 59

pacientes desarrollaron FO persistente, 9 desarrollaron FO transitorio y 2 pacientes fallecieron sin FO. En estos dos pacientes la causa de la muerte fue un episodio de aspiración aguda con paro cardiaco y una arritmia cardiaca maligna.

La edad muy avanzada (mayor o igual de 85 años), la comorbilidad, el sobrepeso, la obesidad, la necrosis pancreática y la cirugía dentro de los 30 primeros días se asociaron a un aumento de la mortalidad a los 30 días tanto en el modelo no ajustado como en el análisis multivariante de regresión de Cox. La PA recurrente se asoció a una reducción de la mortalidad a los 30 días en el análisis no ajustado, pero no en el análisis multivariante.

La comorbilidad, la obesidad, la necrosis pancreática, la necrosis peripancreática, la infección de la necrosis pancreática y la cirugía dentro de los 30 primeros días se asociaron con un aumento del desarrollo de FO persistente tanto en el modelo no ajustado como en el análisis multivariante. El sobrepeso se asoció a un aumento de FO persistente en el análisis no ajustado, pero no en el análisis multivariante. La edad avanzada no se asoció a un aumento del FO persistente ni en el análisis no ajustado ni en el multivariante.

La estancia hospitalaria media fue de 7 días. Una estancia hospitalaria mayor o igual de 13 días se consideró una estancia prolongada dado que representaba el percentil 75. La presencia de necrosis pancreática, necrosis peripancreática, infección de la necrosis pancreática, FO transitorio y persistente y el tratamiento invasivo se asociaron a una estancia hospitalaria prolongada en el análisis simple y en el análisis multivariante de regresión logística. La comorbilidad, la obesidad y la edad no se asociaron con una estancia hospitalaria prolongada en este modelo estadístico.

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

Original Article

United European Gastroenterology Journal
2018, Vol. 6(10) 1508–1518

DOI: 10.1177/2050640618798155
journals.sagepub.com/home/ueg
SAGE

Influence of age, body mass index and comorbidity on major outcomes in acute pancreatitis, a prospective nation-wide multicentre study

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Abstract

Background: There are few large prospective cohort studies evaluating predictors of outcomes in acute pancreatitis.
Objectives: The purpose of this study was to determine the role of age and co-morbid disease in predicting major outcomes in acute pancreatitis.

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Methods: Data points were collected according to a predefined electronic data collection form. Acute pancreatitis and its complications were defined according to the revised Atlanta classification. Univariable and multivariable analyses were conducted using Cox proportional hazard regression and multiple logistic regression.
Results: From June 2013–February 2015, 1655 adult patients were recruited from 23 centres across Spain. Co-morbid disease, obesity, open surgical necrosectomy within 30 days, and pancreatic necrosis were independently associated with both 30-day mortality and persistent organ failure ($p < 0.05$ for all). Age was not associated with persistent organ failure, however the extreme of age (>85 years) was associated with mortality ($p < 0.05$). Co-morbid disease and obesity were not independently associated with a prolonged length of stay or other markers of morbidity on adjusted analysis ($p > 0.05$).
Conclusion: Comorbidity and obesity are important determinates of mortality and persistent organ failure in acute pancreatitis, but in the absence of organ failure they do not appear to independently contribute to morbidity. This has important implications for severity classification and predictive models of severity in acute pancreatitis.

Keywords
Acute pancreatitis, mortality, morbidity, organ failure, comorbidity, comorbidities

Received: 2 May 2018; accepted: 7 August 2018

Introduction

Approximately 70% of patients with acute pancreatitis (AP) have mild disease and are discharged within a week, and only a minority of patients suffer from mortality during admission or develop significant morbidity requiring a longer hospital stay.[1]

The key determinants of morbidity and mortality in AP are organ failure (OF) and infected pancreatic necrosis (IPN). While the revised Atlanta classification (RAC) of 2012 defined severe AP as persistent organ failure (POF), the determinant-based classification (DBC) defined the presence of either POF or IPN as severe AP.[2,3] Despite an exacerbation of comorbid disease being defined as moderately severe AP in the RAC, there is a paucity of data evaluating the impact of comorbid disease on severity in AP.[4,5] There have been a large number of studies evaluating a host of various clinical markers as predictors of severity in AP.[6–9] However, the majority of these studies have either been in a single centre, had a small sample size or were derived from large administrative databases, thus suffering from problems with generalisability and reproducibility. In addition, few studies have incorporated comorbid disease into their clinical models when evaluating determinates of severity.

The primary aims of this study were two-fold. Firstly, to evaluate the influence of age, elevated body mass index (BMI), comorbid disease and a number of known predictors of severity on mortality and OF. Secondly, to evaluate the impact of elevated BMI and comorbid disease on both length of stay (LOS) and other markers of morbidity in AP.

Methods

The Atlantis project, a prospective cohort study, was created under the auspices of the Spanish Association of Pancreatology (AESPANC) and the Spanish Association of Gastroenterology (AEG), to ascertain the role of age, obesity and comorbidity on the course of AP as well as to validate and compare the determinants of severity and the severity classifications. The present study is focused on the first aim. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval from the institutional review board at the principal investigator's centre, Comité ético de investigación clínica del Hospital General Universitario de Alicante on 29 June 2014. The study was also approved by the relevant local ethical committee at each centre. Consent by the patient or their healthcare advocate was required for enrolment in the study.

Patients

Adult (≥18 years) patients with AP were prospectively enrolled at 23 Spanish centres (20 tertiary referral centres and three community centres) from June 2013–February 2015. AP was defined in accordance with the RAC.[2] Patients with documented chronic pancreatitis were excluded. Each centre had one to two gastroenterologists or surgeons responsible for recruiting the patients and collecting data, and a radiologist, blinded to the clinical course and outcomes, responsible for the description of local complications on computerised tomography (CT) imaging. CT imaging was not pursued in those patients with mild AP (self-limited

abdominal pain, absence of clinical and/or laboratory markers of systemic inflammatory response, and successful oral refeeding). We assumed that these patients did not have local complications.

Definitions

Comorbidity was defined according to the Charlson Co-morbidity Index (CCI), age was not included in the score.[10]

BMI, OF, transient organ failure (TOF), POF, inpatient mortality and LOS are defined in Supplementary Material Methods.

The radiologists at each centre recorded the presence of parenchymal and extrapancreatic necrosis based on the RAC definitions. IPN was defined as either parenchymal and/or extrapancreatic seen on CT with a positive culture obtained from the (peri) pancreatic bed.[11]

Interventions were defined as the need for open surgical necrosectomy, transmural endoscopic drainage and/or necrosectomy of (peri) pancreatic collections or radiologically placed percutaneous drain during hospitilization.

Nutritional support was defined as the need for nasoenteric (NE) supplementary feeding or the need for total parenteral nutrition (TPN).

Statistical analysis

Continuous and categorical data were compared between groups using standard parametric and non-parametric tests. Time to event analysis was conducted using the Kaplan-Meier method with log rank testing. Censoring was performed at discharge from hospital. Multivariable Cox proportional hazard regression analyses were performed to evaluate the factors associated with 30-day inpatient mortality and POF. OF was not included in the model for mortality as OF is a known intermediary variable for mortality in AP, thus its inclusion in a mortality models result in an over-adjustment bias.[12] A description of how continuous variables were modelled and how missing data was handled is provided in the supplementary material methods statistical analysis. Multivariable logistic regression analysis was performed to determine the factors associated with a prolonged length of admission (top 25th centile). The results are presented as estimated hazard ratio (HR) or odds ratio (OR) with respective 95% confidence interval (CI) and p values. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 13 (College Station, Texas, USA).

Results

A total of 1655 adult ($\geq$18 years of age) patients were admitted during the study period. Demographic details of the cohort are described in table 1. Patients who died during admission were more likely to be of advanced age and have higher comorbidity ($p < 0.05$). The median (P25, P75) day of mortality was 7 (5, 12) and onset of POF was 2 (1, 7). Figure 1 represents a histogram for the timing of mortality, onset of POF and onset of any OF.

Of the 70 inpatient deaths, 59 patients had POF, nine had TOF and two died without OF. The cause of mortality in the nine patients who died of TOF is as follows: two patients died of sudden death, two died due to septic shock, one patient has an acute aspiration event, one patient had a stroke, one patient had an acute exacerbation of chronic obstructive lung disease and the cause of death was not reported in two patients. The two patients who did not have OF died of an acute aspiration event with subsequent cardiac arrest and the sudden onset of a fatal cardiac arrhythmia, respectively. These patients were 83 and 91 years old on admission, respectively.

30-Day inpatient mortality

Supplementary Material Figure 1 presents the Kaplan-Meier curves for 30-day inpatient mortality. Advanced age, higher CCI and BMI categories, parenchymal necrosis and open surgical necrosectomy within 30 days of presentation were all associated with increased risk of 30-day inpatient mortality on unadjusted and multivariable cox regression analysis (Figure 2 and Supplementary Material Table 1). Recurrent acute pancreatitis (RAP) was associated with a reduced risk of mortality on unadjusted ($p = 0.047$) but not multivariable Cox regression analysis ($p = 0.092$). Isolated peripancreatic necrosis and IPN were not associated with 30-day inpatient mortality on unadjusted and multivariable cox regression analysis ($p > 0.05$). Alcohol aetiology was not associated with 30-day inpatient mortality on an unadjusted Cox regression analysis ($p > 0.05$) or in a multivariable Cox regression analysis, adjusted for the variables presented in Supplementary Material Table 1 ($p > 0.05$), data not shown.

When the same multivariable Cox model was applied to total inpatient mortality, the model fit was superior for 30-day inpatient mortality as compared to total inpatient mortality (AIC: 592.65 vs 723.77). In addition, there was a violation of the proportional hazards assumption for the total inpatient mortality model (global test based on Schoenfeld residuals, $p = 0.049$).

Table 1. Demographics of acute pancreatitis cohort.

	Total 1655	Survivor 1585	Non survivor 70	*p*	No POF 1534	POF 121	*p*
Demographics and clinical details							
Age, mean (SD)	64.5 (17.3)	64.1 (17.3)	72.9 (15.2)	<0.001	64.2 (17.4)	67.9 (16.3)	0.022
Male sex, *n* (%)	891 (53.8)	854 (53.9)	37 (52.9)	0.867	823 (53.7)	68 (56.2)	0.636
Transferred, *n* (%)	105 (6.3)	99 (6.3)	6 (8.6)	0.435	90 (5.9)	15 (12.4)	0.01
Aetiology, *n* (%)							
Gallstone	981 (59.3)	941 (59.5)	40 (57.1)	0.354	909 (59.3)	72 (59.5)	0.759
Alcohol	251 (15.2)	244 (15.4)	7 (10)		236 (15.4)	15 (12.4)	
Idiopathic	235 (14.2)	221 (14.0)	14 (20)		215 (14.0)	20 (16.5)	
Other	188 (11.4)	179 (11.3)	9 (12.9)		174 (11.3)	14 (11.6)	
History of acute pancreatitis, *n* (%)	424 (25.6)	415 (26.2)	9 (12.9)	0.012	405 (26.4)	19 (15.6)	0.007
CCI, median (P25, P75)	0 (0, 1)	0 (0, 1)	1 (0, 3)	<0.001	0 (0, 1)	1 (0, 2)	<0.001
BMI category, *n* (%)[a]							
BMI < 25	509 (31.5)	497 (32.1)	12 (18.2)	0.058	488 (32.6)	21 (17.8)	<0.001
BMI 25-< 30	722 (44.7)	687 (44.4)	35 (53.0)		665 (44.4)	57 (48.3)	0.507
BMI≥30	383 (23.7)	364 (23.5)	19 (28.8)		343 (22.9)	40 (33.9)	0.014
Markers of severity on presentation							
BISAP score, mean (±SD)	1.8 (1.0)	1.8 (1.0)	3.3 (0.9)	<0.001	1.8 (1.0)	3.0 (1.0)	<0.001
SIRS at presentation, *n* (%)	521 (31.5)	456 (28.8)	65 (92.9)	<0.001	411 (26.8)	110 (90.2)	<0.001
BUN at presentation, mean (±SD)	18.7 (±11.4)	18.4 (±11.0)	26.3 (±15.6)	<0.001	18.2 (±10.7)	25.7 (±17.4)	<0.001
Haematocrit at presentation, mean (±SD)	42.0 (±5.4)	41.9 (±5.3)	44.2 (±7.1)	<0.001	41.9 (±5.2)	43.5 (±7.1)	0.002
Treatment							
Nutrition							
Nasoenteric feeding, *n* (%)	94 (5.7)	75 (4.7)	19 (27.1)	<0.001	49 (3.2)	45 (36.9)	<0.001
Peripheral total parenteral nutrition, *n* (%)	91 (5.5)	77 (4.9)	14 (20.9)	<0.001	65 (4.3)	26 (22.0)	<0.001
Central total parenteral nutrition, *n* (%)	92 (5.6)	66 (4.2)	26 (38.2)	<0.001	41 (2.7)	51 (43.2)	<0.001
Interventions							
Percutaneous drain, *n* (%)	58 (3.5)	40 (2.5)	18 (25.7)	<0.001	22 (1.4)	36 (29.5)	<0.001
Endoscopic, *n* (%)	37 (2.2)	30 (1.9)	7 (10.0)	<0.001	16 (1.0)	21 (17.2)	<0.001
Surgery, *n* (%)	47 (2.8)	24 (1.5)	23 (32.9)	<0.001	13 (0.9)	34 (27.9)	<0.001
Outcomes							
Necrosis							
Sterile parenchymal and/or peripancreatic necrosis	153 (9.2)	137 (8.6)	16 (22.9)	<0.001	122 (8)	31 (25.6)	<0.001
Sterile isolated peripancreatic necrosis	68 (4.1)	64 (4.0)	4 (5.7)	0.529	60 (3.9)	8 (6.6)	0.152
Infected pancreatic necrosis (parenchymal and/or peripancreatic necrosis)	59 (3.6)	39 (2.5)	20 (28.6)	<0.001	22 (1.4)	37 (30.6)	<0.001
ICU admission, *n* (%)	126 (7.6)	77 (4.9)	49 (70)	<0.001	40 (2.6)	86 (70.5)	<0.001
Organ failure							
Transient, *n* (%)	121 (7.3)	112 (7.1)	9 (12.9)	0.069	N/A	N/A	N/A
Persistent, *n* (%)	113 (6.8)	54 (3.4)	59 (84.3)	<0.001	N/A	N/A	N/A
Multiorgan failure, *n* (%)	93 (5.6)	43 (2.7)	50 (71.4)	<0.001	N/A	N/A	N/A

BISAP: bedside index of acute pancreatitis; BMI: body mass index; BUN: blood urea nitrogen; CCI: Charlson comorbidity index; ICU: intensive care unit; P25: 25th percentile; P75: 75th percentile; POF: persistent organ failure; SD: standard deviation.
[a]Based on the BMI from 1614 patients.

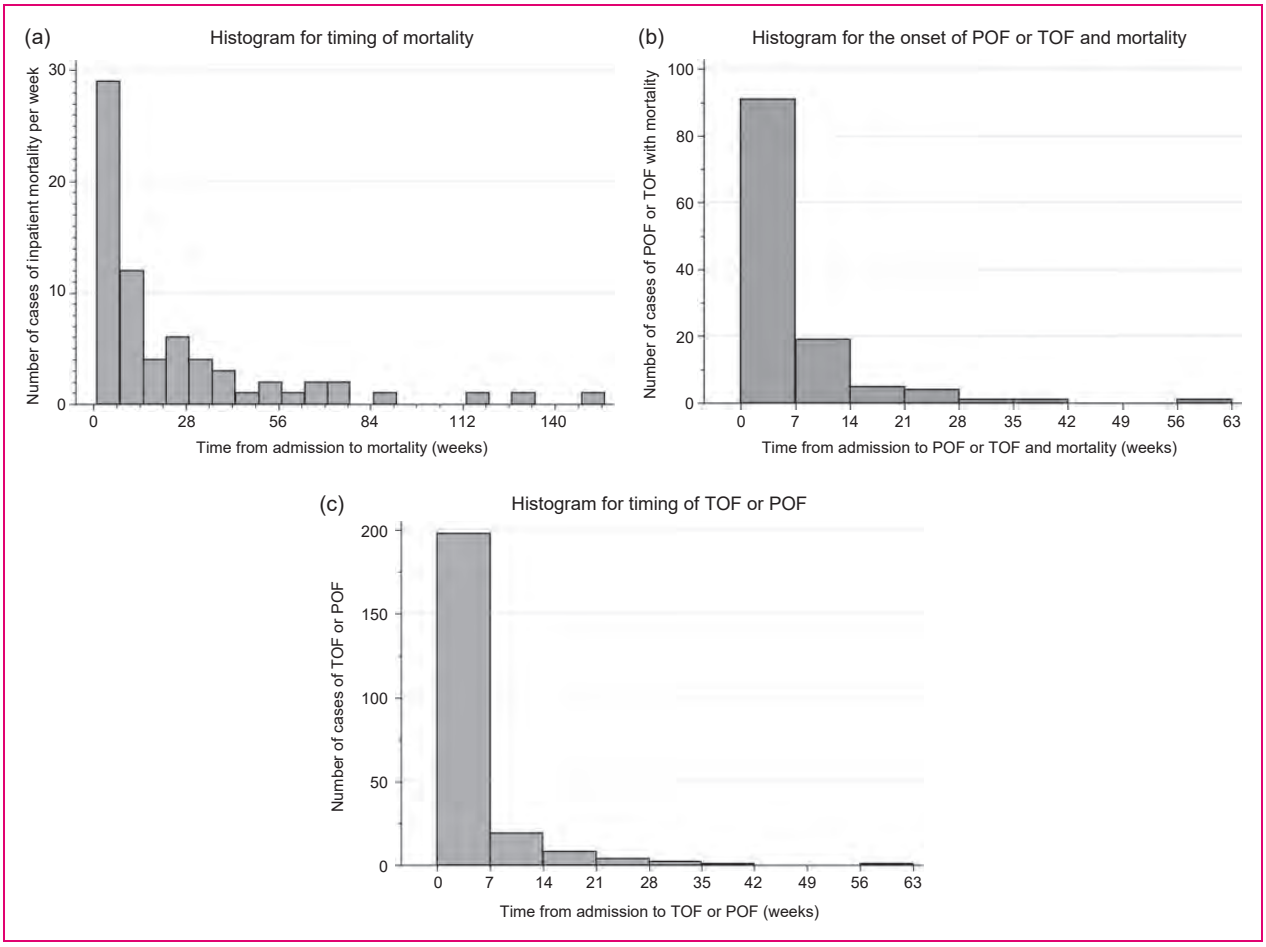

Figure 1. (a) Histogram for timing of mortality in weeks; (b) histogram for the onset of persistent organ failure (POF); (c) histogram for the onset of transient organ failure (TOF) or POF.

POF

A total of 121 patients developed POF (including TOF in non-survivors) during admission. Supplementary Material Figure 2 presents the Kaplan-Meier curves for the probability of developing POF. Higher CCI categories, obesity, parenchymal necrosis, isolated peripancreatic necrosis, IPN and open surgical necrosectomy within 30 days of presentation were all associated with increased risk of developing POF in unadjusted and multivariable cox regression models (Figure 3 and Supplementary Material Table 2). Being overweight was associated with an increased risk of POF on unadjusted but not multivariable Cox regression analysis. Advanced age was not associated with developing of POF on unadjusted or multivariable Cox regression analysis. Alcohol aetiology was not associated with developing POF on unadjusted Cox regression analysis ($p > 0.05$) or on multivariable Cox regression analysis, adjusted for the variables presented in Supplementary Material Table 2 ($p > 0.05$, data not shown).

Length of stay

The median (P25, P75) LOS for all patients was 7 (5, 12) days. LOS of ≥ 13 days was chosen as the cutoff point to mark a prolonged LOS as it represented the top 25th centile for LOS. Prolonged LOS was evaluated with a single and multivariable logistic regression analysis (Figure 4 and Supplementary Material Table 3). The presence of parenchymal necrosis, isolated peripancreatic necrosis, IPN, TOF, POF and the need for endoscopic or surgical intervention and percutaneous drains were associated with a prolonged LOS on both single and multivariable logistic regression analysis ($p > 0.05$, data not shown). Inpatient mortality was associated with a reduced risk of a prolonged LOS on both single and multivariable logistic regression analysis ($p > 0.05$). BMI categories and CCI scores were not associated with a prolonged LOS on single or multivariable logistic regression. Age was not associated with a prolonged LOS on single logistic regression, however on multivariable logistic regression only the

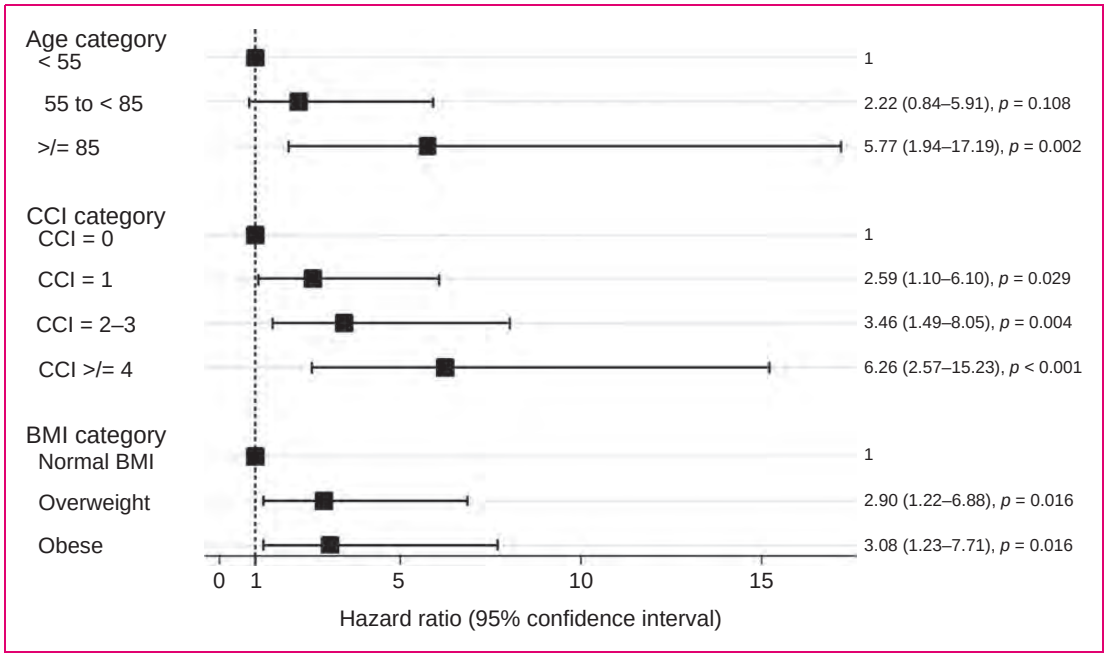

Figure 2. Forest plot of the multivariable Cox model for the development of 30-day inpatient mortality. The Cox model has been adjusted for each listed variable in addition to acute recurrent pancreatitis, parenchymal necrosis, peripancreatic necrosis, infected pancreatic necrosis and early surgery within 30 days of presentation.
BMI: body mass index; CCI: Charlson Comorbidity Index.

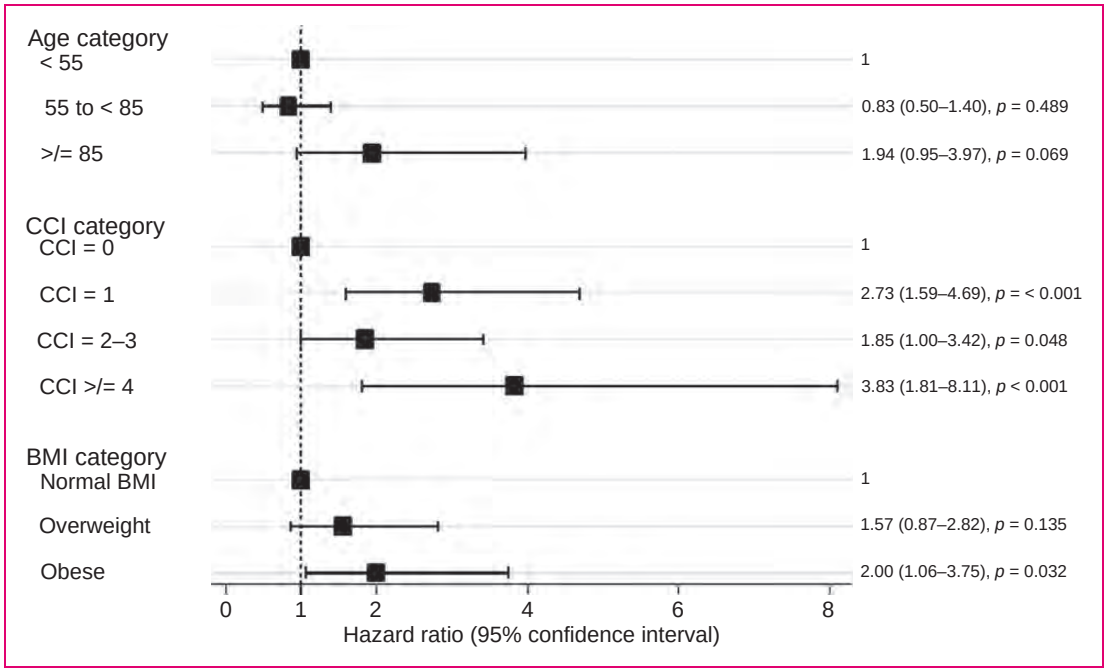

Figure 3. Forest plot of the multivariable Cox model for the development of persistent organ failure. The Cox model has been adjusted for each listed variable in addition to acute recurrent pancreatitis, parenchymal necrosis, peripancreatic necrosis, infected pancreatic necrosis and early surgery within 30 days of presentation.
BMI: body mass index; CCI: Charlson Comorbidity Index.

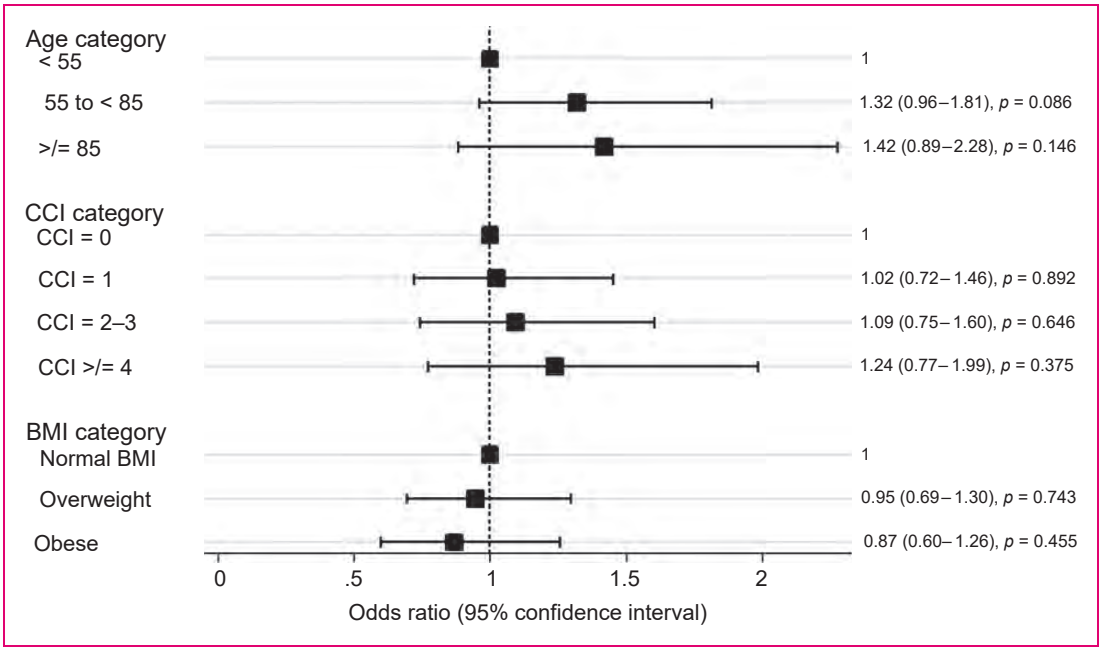

Figure 4. Forest plot of the multivariable logistic regression model for increased length of stay (top 25%). Adjusted for the presence of parenchymal necrosis, peripancreatic necrosis, transient organ failure (TOF), persistent organ failure (POF), percutaneous drains, endoscopic therapy, surgical necrostomy and mortality.
BMI: body mass index; CCI: Charlson Comorbidity Index; OF: organ failure; OR: odds ratio.

extreme of age (age>85 years) was positively associated with a prolonged LOS.

A sensitivity analysis was performed to evaluating LOS in the cohort of survivors who did not develop TOF, POF or mortality ($n = 1419$). After adjusting for the variables listed in Supplementary Material Table 3 (excluding: TOF, POF and mortality) BMI and CCI categories were not associated with a prolonged LOS (Supplementary Material Table 4).

Need for intervention and presence of pancreatic necrosis

BMI categories, CCI scores and age were not independently associated with the need for intervention or nutritional support on multivariable logistic regression adjusted for each predictor variable in addition to TOF and POF ($p > 0.05$, data not shown). On simple logistic regression advanced age was associated with a lower prevalence of peripancreatic or parenchymal necrosis on CT (age <55 vs age ≥85, OR (95% CI) 0.455 (0.279–0.766), $p = 0.003$). BMI categories and CCI scores were not associated with the prevalence of necrosis on CT on simple logistic regression ($p > 0.05$, data not shown).

A sensitivity analysis was performed to evaluating interventions in the cohort of survivors who did not develop TOF or POF ($n = 1419$). After adjusting for the variables listed in Supplementary Material Table 3 (excluding: TOF, POF and mortality), BMI and CCI categories were not associated with the need for intervention or nutritional support ($p > 0.05$, data not shown).

Discussion

The present study has many important findings. Firstly, comorbid disease, elevated BMI, open surgical necrosectomy within the first 30 days of presentation and pancreatic necrosis are independently associated with both 30-day inpatient mortality and POF, while only the extreme of age (>85 years old) was associated with 30-day inpatient mortality but not POF. Secondly, after adjusting for OF and other markers of morbidity, comorbid disease and elevated BMI were not independently associated with a prolonged LOS, a marker of morbidity.

Comorbidity has been demonstrated to be a strong independent risk factor for mortality and morbidity across both a host of individual medical diagnosis and in unselected patients requiring acute hospital admission.[13–15] While many tools exist, the CCI is the most extensively utilised clinical tool for assessing the impact of comorbid disease on clinical outcomes.[16] Considering the importance of comorbidity in predicting outcomes for other diseases, there is an overall paucity of literature regarding the role of comorbidity in AP. Apart from the limited recording of comorbid

disease in the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, comorbid disease is not incorporated into clinical predictive models of severity in AP.[17] In a study of an administrative database, the individual comorbidities contained within the CCI were found to be associated with mortality and the development of multiorgan failure (MOF) within the first two weeks of admission with AP.[4] This study was limited by it retrospective nature, its reliance on an administrative data base with ICD 9 codes and the lack of utilization of survival analysis. Comorbidity was demonstrated to be a strong independent predictor of 30-day inpatient mortality and POF in the present study with increasing levels of comorbidity being associated with a progressively higher risk of 30-day inpatient mortality and POF.

Obesity is a known validated predictor of mortality, OF and local and systemic complications in patients with AP.[9] Elevated levels of intrapancreatic fat are associated with increased BMI.[18,19] In addition elevated BMI is associated with elevated visceral fat which surrounds the pancreas. Pancreatic lipase is thought to induce lipolysis in adipocytes resulting in increased unsaturated fatty acids which in turn drives the inflammatory cascade.[20] Obesity is known to be associated with an excess of medical comorbidities.[21] In the present study being overweight or obese was independently associated with an increased risk of POF and being obese was independently associated with 30-day inpatient mortality even after adjusting for other medical comorbidities. This is in keeping with the intrinsic mechanism of lipolysis associated with elevated BMI.

Older age has been studied extensively as a marker of severity and mortality in AP and is incorporated in the APACHE II score, Ranson score, the bedside index of acute pancreatitis (BISAP) score and the Japanese severity score (JSS) as a marker of severity, with an age range of>45 up to>70 years old being associated with adverse clinical outcomes in these scoring systems.[17,22] Contrary to previously published studies, after adjusting for comorbid disease in the present study, only the very extreme of age (>85 years old) was associated with 30-day inpatient mortality and POF. The likely explanation for this is that advancing age is associated with a higher degree of comorbid diseases, consequently, after adjusting for comorbid disease the relationship between older age and adverse clinical while remaining significant but is no longer as strong.[23] A numerical age does not necessarily reflect a person's underlying health status, a concept embodied by the theory of biological vs chronological age.[24]

The International Association of Pancreatology and American Pancreatic Association evidence-based guidelines describe using host risk factors, such as age, co-morbidity and BMI as part of a three-pronged approach in predicting outcomes of AP. The results described within the present study support the use of co-morbidity and BMI for the risk stratification of patients with AP. In order for these host factors to be adequately incorporated into our management of AP, predictive tools that adequately incorporating these variables will need further development.[25]

Delaying open surgical necrosectomy has been shown to be associated with a reduction in mortality.[26] This has led to the adoption of a step-up approach where a gradual step up from more minimally invasive interventions to an open surgical necrosectomy is performed if necessary. This has been shown to be associated with a reduction in new onset MOF in a randomised controlled trial.[27] Recent mortality data from an international cohort of nearly 2000 patients supports the use of minimally invasive surgical or endoscopic drainage/debridement procedures over open surgical necrosectomy.[28] The higher risk of 30-day inpatient mortality in patients who have open surgical necrosectomy within 30 days of presentation in the current study further highlights that patients should not undergo early surgical necrosectomy as the standard of care in 2017.

Both isolated peripancreatic necrosis and parenchymal necrosis (±peripancreatic necrosis) are known predictors of morbidity, POF and mortality in AP, the results of the present study validate these finding.[2,29] Interestingly, IPN was not associated with 30-day inpatient mortality but was associated with overall hospital mortality, supporting the published literature that deaths due to IPN occur later in the disease.[30] This is an important yet challenging factor to consider when developing clinical predictive models of mortality in AP since assessing 30-day mortality is standard for most diseases, and using total mortality during the entire length of admission to incorporate late mortality events associated with IPN may result in variables violating the assumptions made in survival analysis, as was the case in the present study.

Importantly comorbidity and elevated BMI were not associated with increased LOS or other markers of morbidity on adjusted analysis, incorporating OF. Consequently, co-morbid disease and elevated BMI can be seen to increase hospital morbidity by increasing the risk of OF, but in the absence of OF, co-morbid disease does not increase morbidity (Figure 5). Inclusion of 'exacerbation of co-morbid disease' in the moderate severity of the RAC is potentially redundant, as exacerbation of co-morbid disease resulting in increased morbidity is accounted for by the development of OF which is presently a key component of the RAC. Finally, only the extreme of age was associated with increased LOS. It is possible that increased LOS in this older population may be a surrogate for

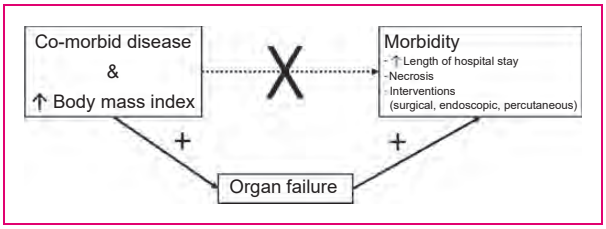

Figure 5. Relationship between elevated body mass index (BMI), co morbidity, persistent organ failure (POF) and morbidity.

living alone and needing to be at a more advanced stage in their rehabilitation or have a social support package in place prior to discharge. Data from the UK reports that 50% of the UK population older than 75 years lives alone, while 26% of 65–74 year olds and 16% of 45–64 year olds live alone.[31] From a practical viewpoint, patients older than 85 years are generally not included in clinical trials.

The main strength of the present study is that it is a large multicentre, prospective study that included tertiary and non-tertiary centres with predefined definitions and data collection sheet. Secondly, survival analysis was utilised for the primary analysis, POF and 30-day mortality. In comparison to standard logistic regression which has been used in most epidemiological studies of AP, this type of analysis is more powerful, allows for censoring and is commonly used in epidemiological studies of major disease outcomes and 30-day mortality.[32,33] Finally, as opposed to using previously published cut off points for age and CCI, these variables were individually modelled in order to achieve the best fit of these variables for this data set. There are a number of limitations in the present study. Imaging data was evaluated by a local radiologist and not a centralised radiologist. Evaluating for the present of peripancreatic and parenchymal necrosis is known to be associated with a high inter-reader variability.[34] However, the results for necrosis are broadly in keeping with the published literature arguing against significant flaws in this data. Lastly, supportive measures such as fluid resuscitation which have been associated with major clinical outcomes were not accounted for. While this may have impacted the results, it does allow for the broad generalisability of the studies current findings.

In conclusion, comorbid diseases, including BMI are significant determinates of POF and mortality in AP and their inclusion in clinical models and predictive scores evaluating major clinical outcomes in AP is important. After accounting for OF, comorbid disease, including BMI is not associated with a prolonged LOS or other markers of morbidity, thus inclusion of 'exacerbation of co-morbid disease' in the moderate severity of the RAC may be redundant.

Summary of the established knowledge on this subject

- Obesity is associated with organ failure in clinical studies of acute pancreatitis and has been shown to be associated with mortality in a meta-analysis.
- There is a limited description of the role of co-morbid disease in the development of morbidity, organ failure and mortality in acute pancreatitis.

What are the significant and/or new findings of this study?

- Comorbid disease is independently associated with both organ failure and morality in acute pancreatitis.
- Co-morbid disease and obesity are not independently associated with markers of morbidity, including: length of hospital stay, development of necrosis (pancreatic, peripancreatic or infected) and interventions (surgery, endoscopy or percutaneous drains).
- Age is not independently associated with persistent organ failure and age is only associated with mortality in the very elderly (>85 years old).

Acknowledgements

For reviewing the manuscript prior to submission, the authors wish to thank Dhiraj Yadav, Division of Gastroenterology, University of Pittsburgh Medical Center, Pittsburgh, USA.

The participating investigators were:

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Declaration of conflicting interests

Vikesh Singh is a consultant to Abbvie, Akcea and Ariel Precision Medicine. Enrique de_Madaria is consultant to Mylan. All other authors have no disclosures.

Ethics approval

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval from the institutional review board at the principal investigator's centre, Comitéé tico de investigación clínica del Hospital General Universitario de Alicante on 29 June 2014. The study was also approved by the relevant local ethical committee at each centre.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not_for_profit sectors.

Informed consent

Informed consent by the patient or their healthcare advocate was acquired for all patients enrolled in the study.

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Capítulo 3: Patrones de consumo de grasa en la dieta y curso clínico de la pancreatitis aguda en España.

3.1 Metodología

Se trata de un análisis retrospectivo de los datos de la base prospectiva del proyecto *Atlantis* combinados con los datos del estudio nutricional transversal *ANIBES (Anthropometric data, macronutrients and micronutrients intake, practice of physical activity, socioeconomic data, and lifestyles in Spain).* Las características de la base prospectiva del proyecto *Atlantis* han sido descritas en apartados previos. El objetivo del estudio *ANIBES* fue actualizar la información sobre la ingesta de alimentos y bebidas, el comportamiento y las mediciones antropométricas de los ciudadanos españoles, así como determinar su gasto de energía y hábitos de ejercicio físico. Para ello se incluyeron en el estudio 2009 ciudadanos españoles [3]. La dieta se estudió utilizando un diario dietético (durante 3 días) registrado en un dispositivo tipo *tablet* más la realización de un cuestionario telefónico sobre la dieta en las últimas 24 horas. Se explicó a los participantes que la dieta durante esos 4 días tenía que ser representativa de su dieta en los últimos años. El estudio *ANIBES* dividió a España en 9 regiones: Barcelona, Islas Canarias, Centro, Levante, Madrid, Noroeste, Noreste, Norte-Centro y Sur.

De la base original del estudio *ANIBES* se extrajeron los datos sobre el consumo de lípidos, ácidos grasos saturados (SFAs), ácidos grasos insaturados (UFAs) monoinsaturados (MUFAs) y poliinsaturados (PUFAs). Según el estudio *ANIBES* la ingesta media de calorías en España es de 1.810 kcal/día, que incluye un 38.5% de lípidos globales, un 11.7% de SFAs y un 23.43% de UFAs (de ellos un 16.8% de MUFAs y un 6.63% de PUFAs) [4]. Los pacientes con PA del proyecto *Atlantis* provenientes de regiones con una ingesta de un tipo de ácido graso mayor que la media nacional fueron considerados altos consumidores en cuanto a ese tipo de ácido graso, mientras que los pacientes provenientes de regiones con una ingesta menor que la media nacional fueron considerados como bajos consumidores. Las diferencias de consumo de PUFAs entre las diferentes regiones de España fueron mínimas así que no incluimos este tipo de ácido graso en el análisis.

En el análisis estadístico, la asociación entre el consumo alto o bajo de cada ácido graso con las variables de resultado (*outcomes)* se evaluó usando la prueba de chi-cuadrado y un análisis de regresión logística para el análisis multivariante. Se usaron dos modelos de análisis multivariante. El primero modelo incluyó la edad, la comorbilidad según el Índice de Comorbilidad de Charlson [2] (con un punto de corte ≥ 3), el sexo, la etiología alcohólica y la PA recurrente. El segundo modelo incluyó las variables del primer modelo más la obesidad.

3.2 Resultados

Las características basales de los 1655 pacientes del proyecto *Atlantis* se han descrito en los capítulos previos. Cabe destacar que el 24% de estos pacientes fueron obesos. En el análisis univariante, los pacientes con PA provenientes de regiones con un alto consumo de lípidos en general tuvieron significativamente más frecuencia de PA moderada-grave y una tendencia no significativa a presentar más complicaciones locales. Los pacientes de regiones con un alto consumo de UFAs tuvieron significativamente más complicaciones locales, FO persistente, mortalidad y PA moderada-grave. Pertenecer a una región con un alto consumo de MUFAs se asoció significativamente a más complicaciones locales y PA moderada-grave. El diferente consumo de SFAs no se asoció a ninguna variable de resultado.

En el análisis multivariante, los pacientes de regiones con un alto consumo de lípidos en general tuvieron más frecuencia de PA moderada-grave en el modelo multivariante que no incluyó la obesidad, pero al incluir la obesidad en el modelo perdió la asociación significativa. Los pacientes provenientes de regiones con un alto consumo de UFAs tuvieron significativamente más complicaciones locales, FO persistente, mortalidad y PA moderada-grave en el modelo sin obesidad, después de incluir la obesidad en el modelo se mantuvo la asociación con el FO persistente y se mostró una tendencia no significativa para el resto de las variables. Los pacientes de regiones con un alto consumo de MUFAs presentaron significativamente más complicaciones locales y PA moderada-grave, manteniéndose la significación para PA moderada-grave tras incluir la obesidad en el modelo. El diferente consumo (alto o bajo) de SFAs no se asoció a ninguna variable de resultado.

frontiers in Medicine

ORIGINAL RESEARCH
published: 09 April 2020
doi: 10.3389/fmed.2020.00126

Dietary Fat Patterns and Outcomes in Acute Pancreatitis in Spain

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OPEN ACCESS

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Reviewed by:
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Specialty section:
This article was submitted to Gastroenterology, a section of the journal Frontiers in Medicine

Received: *08 November 2019*
Accepted: *20 March 2020*
Published: *09 April 2020*

Citation:
García-Rayado G, Varela-Moreiras G, Lanas Á, Ferrández Á, Balza-Lareu N, Cervera JI, Bodenlle-Bello MP, Argüelles-Arias AM, Latorre P, Udaondo-Cascante MA, Soria-de-la-Cruz MJ, Lariño-Noia J, García-Figueiras R, Gil-García-Ollauri C, Ituarte-Uriarte R, Rosales-Alexander CL, Soriano J, Rodríguez-Peláez M, Mesa-Álvarez A, Oblitas E, Menso MM, Bertoletti F, Rodríguez-Prada JI, Guzmán-Suárez S, Closa D and de-Madaria E (2020) Dietary Fat Patterns and Outcomes in Acute Pancreatitis in Spain. Front. Med. 7:126. doi: 10.3389/fmed.2020.00126

Background/Objective: Evidence from basic and clinical studies suggests that unsaturated fatty acids (UFAs) might be relevant mediators of the development of complications in acute pancreatitis (AP). Objective: The aim of this study was to analyze outcomes in patients with AP from regions in Spain with different patterns of dietary fat intake.

Materials and Methods: A retrospective analysis was performed with data from 1,655 patients with AP from a Spanish prospective cohort study and regional nutritional data from a Spanish cross-sectional study. Nutritional data considered in the study concern the total lipid consumption, detailing total saturated fatty acids, UFAs and monounsaturated fatty acids (MUFAs) consumption derived from regional data and not from the patient prospective cohort. Two multivariable analysis models were used: (1) a model with the Charlson comorbidity index, sex, alcoholic etiology, and recurrent AP; (2) a model that included these variables plus obesity.

Results: In multivariable analysis, patients from regions with high UFA intake had a significantly increased frequency of local complications, persistent organ failure (POF), mortality, and moderate-to-severe disease in the model without obesity and a higher frequency of POF in the model with obesity. Patients from regions with high

MUFA intake had significantly more local complications and moderate-to-severe disease; this significance remained for moderate-to-severe disease when obesity was added to the model.

Conclusions: Differences in dietary fat patterns could be associated with different outcomes in AP, and dietary fat patterns may be a pre-morbid factor that determines the severity of AP. UFAs, and particulary MUFAs, may influence the pathogenesis of the severity of AP.

Keywords: acute pancreatitis, diet, fat intake, obesity, unsaturated fatty acids

INTRODUCTION

Acute pancreatitis (AP) is a common health issue (1). While most patients have a mild disease course, one-third experience local and/or systemic complications that produce an increase of morbidity (2). Furthermore, patients with systemic complications have a higher mortality, which is as high as 50% among patients with persistent (>48 h) organ failure (POF) (2). The factors that determine the development of complications in AP are currently poorly understood. Obesity, particularly visceral adiposity, is associated with local complications, with systemic complications, and with increased risk of death (3–5). *In vitro* experiments using acinar cells of the pancreas have shown that unsaturated fatty acids (UFAs) are associated with inflammation and necrosis, while saturated fatty acids (SFAs) are not harmful. These experiments suggest that UFAs produce necrosis of acinar pancreatic cells and uncontrolled UFA release results in high UFA levels in the bloodstream and is associated with kidney failure and with cell damage in lung alveoli (6, 7). UFAs have been detected in pancreatic necrosis collections (6–9). Furthermore, oleic acid chlorohydrin, a halogenated product derived from monounsaturated oleic acid, was recently described as a blood marker and mediator of complications in a rat model of AP (10) and in patients with AP (11). Thus, UFA-mediated toxicity seems to be a key pathway in determining complications of AP (11, 12). Preceding studies have suggested that diet affects body fatty acid composition. In animal models, mice with diets with different content in oleic acid and linoleic acid show these differences on the composition of fatty acids of their tissues. Studies in humans also show this association (13, 14). Consequently, it is possible that the changes induced by dietary UFAs can modulate the severity of AP. To our knowledge, there are no clinical studies studying this relationship. This study aimed to compare clinical course of disease of AP in regions of Spain that have different dietary fat intake patterns.

MATERIALS AND METHODS

This was a retrospective analysis of data from a prospective cohort study, the Atlantis Project, plus data from a cross-sectional study, the ANIBES (Anthropometric data, macronutrients and micronutrients intake, practice of physical activity, socioeconomic data, and lifestyles in Spain) study.

The Atlantis Project was endorsed by the Spanish Association of Pancreatology (AESPANC) and by the Spanish Association of Gastroenterology (AEG). It aimed to validate and compare the determinants of AP severity and the severity classifications of AP (2) as well as to ascertain the role of comorbidity in the course of AP (4). Described in detail elsewhere (2), the Atlantis project was a 23-center nationwide prospective study which analyzed 1,655 patients with AP recruited from June 2013 to February 2015. All centers were tertiary care hospitals with availability of critical care. In Spain, there is a public healthcare system and citizens have similar access with similar quality of care in the different regions of the country. The project was carried out following the rules of the Declaration of Helsinki of 1975. The study required written informed consent and was approved by the Institutional Review Boards (IRBs) of the participating centers. This new analysis was also approved by the central IRB of the Atlantis study, namely the *Comité Ético de Investigación con Medicamentos del Hospital General Universitario de Alicante (PI2018-102)*. For the diagnosis of AP, two or more criteria had to be fulfilled: (A) typical upper abdominal pain; (B) serum amylase and/or lipase levels that were at least three times greater than the upper limit of normal; and (C) imaging compatible with AP (15). Patients with a diagnosis of chronic pancreatitis were excluded. Patient outcomes were recorded during their hospital stay, and the following data were retrieved from the study database for this analysis: local complications (acute peripancreatic fluid collections or pancreatic and/or peripancreatic necrosis), POF, mortality (in-hospital mortality), and disease severity (moderate-to-severe disease). These were defined according to the revised Atlanta classification (15). Obesity was defined as body mass index $\geq$30 kg/m^2.

The aim of the ANIBES study was to update the food and beverage intake, behavior, and anthropometric measurements of the Spanish citizens, as well as to determine their energy expenditure and physical exercise habits (sample: 2009 citizens) (16). Diet was studied using a dietary diary (during 3 days) recorded on a tablet device plus a 24-h dietary recall. The participants were explained that the diet during those 4 days had to be representative of their diet of the past years. The ANIBES study divided Spain into nine regions: Barcelona, Canary Islands, Central, Levant, Madrid, North-East, North-West, North-Central, and South (16). Data regarding the consumption

Abbreviations: AP, acute pancreatitis; APFC, acute peripancreatic fluid collection; BMI, body mass index; CCI, Charlson comorbidity index; H, High consume; IQR, interquartile range; IRB, Institutional Review Board; L, Low consume; MUFA, monounsaturated fatty acid; OR, odds ratio; POF, persistent organ failure; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; UFA, unsaturated fatty acid.

of lipids, SFAs, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) were retrieved from the original ANIBES database. According to ANIBES, the Spanish mean daily caloric intake is 1,810 kcal/day, including 38.5% from lipids (overall), 11.7% from SFAs, and 23.43% from UFAs (16.8% from MUFA and 6.63% from PUFAs) (17). Patients in the Atlantis Project from regions that had intake levels that were higher than the national mean values were considered to be high consumers regarding that specific type of fatty acid, while patients from regions that had intake levels that were lower than the Spanish mean values were classified as low consumers. For example, the national mean intake of UFAs is 23.6% (mean percentages of total caloric intake) and the mean intake of UFAs in North-Central region of Spain is 24.2%. Therefore, patients in the Atlantis Project from North-Central region were considered to be high consumers of UFAs. The differences in consumption of PUFAs in the different regions of Spain are minimal, so we have not included this type of fatty acid in the analysis.

Statistics

Continuous data were analyzed for normality by the Shapiro-Wilk test and were summed-up using means and standard deviations or medians and interquartile ranges (IQRs) depending on the variable distribution. Qualitative variables were expressed as number (*n*) and percentage (%). The association of low or high fat consumption according to region and outcome was investigated using a chi-square test or Fisher's exact test if necessary and using binary logistic regression analysis for multivariable analysis. Two multivariable analysis models were used: (1) a model without obesity that included age, comorbidity (according to the Charlson comorbidity index, cutoff $\geq$3) (18), sex, alcoholic etiology, and recurrent AP ($\geq$1 previous episode); (2) a model with obesity that included all of these variables plus obesity. The adjusted odds ratios (ORs) were calculated. Statistical calculations were done using SPSS 21.0 (IBM, Armonk, NY, USA).

RESULTS

Table 1 shows the detailed baseline characteristics and outcomes of the 1,655 patients with AP. The patients had a median age of 66 years; 54% were male, 24% were obese, 60% had gallstone etiology, 27% had local complications, 7% had POF, and 4% died. Regarding these baseline characteristics, there were no significant differences between the different regions of Spain ($p > 0.05$). **Supplementary Table 1** shows the caloric profile of lipid intake of the Spanish population as stratified by region according to the ANIBES study. **Supplementary Table 2** lists the number of medical centers and patients of the Atlantis database in the regions defined in the ANIBES study.

TABLE 1 | Baseline characteristics and outcomes of patients with acute pancreatitis.

Characteristics and outcomes	Overall
N	1,655
Age, years; median (IQR)	66 (51–79)
Male sex, *n* (%)	891 (53.8%)
BMI, kg/m^2	
Median (IQR)	26.8 (24.3–29.7)
BMI < 25	509 (31.5%)
BMI 25–<30 (Pre-Obesity)	722 (44.7%)
BMI ≥ 30 (Obesity)	383 (23.7%)
CCI, points; median (IQR)	3 (1–5)
Liver disease, *n* (%)	120 (7.2%)
Etiology, *n* (%)	
Gallstones	984 (59.5%)
Alcohol	251 (15.2%)
Idiopathic	235 (14.2%)
Other	185 (11.2%)
Recurrent AP, *n* (%)	422 (25.5%)
Local complications, *n* (%)	
Any local complication	444 (26.8%)
APFC	163 (9.8%)
Peri(pancreatic) necrosis	281 (17%)
Persistent organ failure, *n* (%)	113 (6.8%)
Mortality, *n* (%)	70 (4.2%)

IQR, interquartile range (Q1–Q3); BMI, body mass index; CCI, Charlson comorbidity index; AP, acute pancreatitis; APFC, acute peripancreatic fluid collection; Peri(pancreatic) necrosis, pancreatic and/or peripancreatic necrosis.

Univariate Analysis

Table 2 shows outcomes according to lipid intake (univariate analysis). Moderate-to-severe disease was more frequently present in patients from regions with a high overall lipid intake [37 vs. 32.1%, $p = 0.04$], who also showed a non-significant trend toward a higher frequency of local complications [28.4 vs. 24.6%, $p = 0.08$]. Patients from regions with high intake of UFAs had significantly more local complications [28.6 vs. 20.5%, $p = 0.002$], POF [7.7 vs. 3.8%, $p = 0.01$], mortality [4.8 vs. 2.2%, $p = 0.03$], and moderate-to-severe disease [36.7 vs. 29%, $p = 0.007$]. Being from a region with high MUFA intake was significantly associated with more local complications [29.6 vs. 23.9%, $p = 0.009$] and moderate-to-severe disease [38.1 vs. 31.7%, $p = 0.007$]. SFA intake had no effect on outcomes (**Table 2**).

Multivariable Analysis

In multivariable analysis (**Table 3**), patients from regions with high overall lipid intake had significantly more frequent moderate-to-severe disease in the model without obesity [OR = 1.26; 95% CI: 1.02–1.55; $p = 0.034$], but high overall lipid intake was not significant after obesity was included in the model [OR = 1.19; 95% CI: 0.96–1.48; $p = 0.1$]. Patients with AP from regions with high UFA intake had significantly higher rates of local complications [OR = 1.53; 95% CI: 1.15–2.05; $p = 0.004$], POF [OR = 2.1; 95% CI: 1.18–3.74; $p = 0.01$], mortality [OR = 2.37; 95% CI: 1.12–5.03; $p = 0.02$], and moderate-to-severe disease [OR = 1.42; 95% CI: 1.1–1.85; $p = 0.007$] in the model without obesity compared to patients from areas with low UFA intake; after entering the variable obesity into the model, high UFA intake remained a risk factor

TABLE 2 | Outcomes of acute pancreatitis according to regional lipid intake.

Lipid	Intake	Outcomes: *n* (%)			
		Local complications	**Persistent organ failure**	**Mortality**	**Moderate-to-severe AP**
Lipids (overall)	High	278 (28.4%)	71 (7.3%)	43 (4.4%)	362 (37%)
	Low	166 (24.6%)	42 (6.2%)	27 (4%)	217 (32.1%)
	P	0.08	0.4	0.7	**0.04**
SFAs	High	327 (26.9%)	79 (6.5%)	47 (3.9%)	430 (35.4%)
	Low	117 (26.7%)	34 (7.7%)	23 (5.2%)	149 (33.9%)
	P	0.9	0.4	0.2	0.6
UFAs	High	369 (28.6%)	99 (7.7%)	62 (4.8%)	473 (36.7%)
	Low	75 (20.5%)	14 (3.8%)	8 (2.2%)	106 (29%)
	P	**0.002**	**0.01**	**0.03**	**0.007**
MUFAs	High	252 (29.6%)	65 (7.6%)	39 (4.6%)	324 (38.1%)
	Low	192 (23.9%)	48 (6%)	31 (3.9%)	255 (31.7%)
	P	**0.009**	0.2	0.5	**0.007**

Percentages are the proportions of the patients of the whole cohort (high or low consumers) that show each outcome of AP.
SFAs, saturated fatty acids; UFAs, unsaturated fatty acids; MUFAs, monounsaturated fatty acids; High, patients from a region of Spain with a proportion of caloric intake from all lipids or from the indicated types of lipids that was greater than the Spanish national mean; Low, patients from a region of Spain with a proportion of caloric intake from all lipids or from the indicated types of lipids that was lower than the Spanish national mean; AP, acute pancreatitis; P, P-value in the chi-square test (Fisher's exact test was not required).
Bold value indicates P-value statistically significant.

TABLE 3 | Multivariate analysis of high overall lipid intake and lipid subtype intake and outcomes in acute pancreatitis.

Lipid	Model	Adjusted odds ratio			
		Local complications	**Persistent organ failure**	**Mortality**	**Moderate-to-severe AP**
Lipids (overall)	Without obesity	1.21 (0.96–1.53) $P = 0.1$	1.21 (0.82–1.8) $P = 0.3$	1.15 (0.7–1.88) $P = 0.6$	1.26 (1.02–1.55) $\mathbf{P = 0.034}$
	With obesity	1.11 (0.88–1.41) $P = 0.4$	1.23 (0.81–1.87) $P = 0.3$	1.11 (0.66–1.87) $P = 0.7$	1.19 (0.96–1.48) $P = 0.1$
SFAs	Without obesity	0.98 (0.76–1.26) $P = 0.9$	0.87 (0.57–1.32) $P = 0.5$	0.76 (0.45–1.28) $P = 0.3$	1.06 (0.84–1.3) $P = 0.63$
	With obesity	1.01 (0.78–1.3) $P = 0.9$	0.87 (0.57–1.34) $P = 0.5$	0.83 (0.48–1.42) $P = 0.49$	1.11 (0.88–1.4) $P = 0.4$
UFAs	Without obesity	1.53 (1.15–2.05) $\mathbf{P = 0.004}$	2.1 (1.18–3.74) $\mathbf{P = 0.01}$	2.37 (1.12–5.03) $\mathbf{P = 0.02}$	1.42 (1.1–1.85) $\mathbf{P = 0.007}$
	With obesity	1.34 (0.99–1.83) $P = 0.06$	2.4 (1.24–4.71) $\mathbf{P = 0.01}$	2.09 (0.94–4.66) $P = 0.07$	1.27 (0.96–1.67) $P = 0.09$
MUFAs	Without obesity	1.3 (1.03–1.62) $\mathbf{P = 0.025}$	1.36 (0.92–2) $P = 0.1$	1.29 (0.79–2.09) $P = 0.3$	1.33 (1.08–1.63) $\mathbf{P = 0.008}$
	With obesity	1.2 (0.95–1.5) $P = 0.1$	1.37 (0.91–2.06) $P = 0.1$	1.24 (0.75–2.07) $P = 0.4$	1.26 (1.02–1.56) $\mathbf{P = 0.035}$

In the binary logistic regression analysis, the data are reported as adjusted odds ratios (95% confidence intervals) and P-values (reference group: low intake of lipids). Model, the model used for multivariable analysis; Without obesity, the model that included Charlson comorbidity index (cutoff ≥3), sex, alcoholic etiology, and recurrent AP; With obesity, the model that included these same variables plus obesity (body mass index ≥ 30 kg/m^2); SFAs, saturated fatty acids; UFAs, unsaturated fatty acids; MUFAs, monounsaturated fatty acids; AP, acute pancreatitis.
Bold value indicates P-value statistically significant.

for POF [OR = 2.4; 95% CI: 1.24–4.71; $p = 0.01$], showing a non-significant trend for the other outcomes. Patients from regions with high MUFA intake had significantly increased rates of local complications [OR = 1.3; 95% CI: 1.03–1.62; $p = 0.025$] and moderate-to-severe disease [OR = 1.33; 95% CI: 1.08–1.63; $p = 0.008$], and the significance remained for moderate-to-severe disease after entering the variable obesity into the model [OR = 1.26; 95% CI: 1.02–1.56; $p = 0.035$]. SFA intake was not associated with any effect on outcomes (**Table 3**).

DISCUSSION

Obesity is an important factor in AP severity and is associated with worse outcomes (3, 4, 19). The Atlantis prospective cohort study confirmed that obesity is associated with a higher mortality and with a higher incidence of POF (4), and fatty acids could be relevant mediators in the physiopathogenesis of moderate-to-severe AP in obese patients. There is robust evidence from basic research that UFAs are more toxic than SFAs (6, 7, 9, 12, 20–22). Analysis of postmortem tissue from obese patients has shown

that UFAs are the predominant fatty acids in the pancreas, whereas the proportion of SFAs is lower (23, 24). Furthermore, UFAs are the most common (70–75%) non-esterified fatty acids in necrotic pancreatic collections (6–9). The Singh group has performed *in vitro* studies using pancreatic acinar cells and has studied animal models of AP and reports that UFAs are associated with increased inflammation and necrosis, while SFAs are not harmful (6, 7, 21, 22). These experiments suggest that (A) UFAs are the consequence of lipolysis of visceral fat by pancreatic lipases; (B) local UFAs produce necrosis of acinar pancreatic cells; and (C) uncontrolled UFA release results in high UFA levels in the bloodstream and is associated with renal tubular apoptosis (and subsequently with kidney failure) as well as with cell damage in lung alveoli that is similar to that seen in acute respiratory distress syndrome (6, 7, 9, 12, 22). UFAs seem to induce cell death by inhibiting mitochondrial complexes I and V and by increasing intracellular calcium release (6, 25). In addition, in severe AP a vicious cycle of inflammation and increasing oxidative stress is created. UFAs, but not SFAs, are sensitive to oxidative metabolic conditions and can worse this deleterious cycle in AP (26). This role of UFA-mediated lipotoxicity in worsening AP is consistent with the worse outcomes found in hypertriglyceridemic AP and in obese patients with AP (4, 27). On the other hand, studies show that dietary fatty acid patterns may affect body fat composition. Mice fed diets that have higher oleic acid and lower linoleic acid show differences in adipose tissue and fat composition of the pancreas (23). Studies in humans show that the proportion of different fatty acids of adipose tissue and plasma reflects, at least in part, different dietary intake patterns (28–30).

UFAs are more toxic than SFAs, and body fat composition is affected by dietary fatty acid intake. Thus, we hypothesized that regional fat intake patterns could be associated with different outcomes of AP. We also wanted to investigate whether dietary fat patterns had an independent effect on outcomes when we controlled for the presence of obesity. Accordingly, we compared outcomes in patients from regions of Spain with different fat intake levels. To our knowledge, this is the first study of its kind, there are no clinical studies studying this association in Spain or in other countries. Our study found that patients with AP from areas with a high UFA consumption had significantly higher rates of local complications, POF, mortality and frequency of moderate-to-severe AP in univariate analysis; this effect was also observed in multivariable analysis (for all four variables in the model not including obesity and for POF in the model including obesity). Patients from regions with high SFA intake did not have a worse prognosis. It is well-known that POF is the main determinant of severity in AP as reflected by the severe disease category of the revised Atlanta classification, which is defined exclusively by the presence of POF (15). Severe AP entails the greatest morbidity and mortality (2). Taken together, our results suggest that high UFA intake could be an important pre-morbid factor in determining the severity of AP (31).

Concerning the different types of UFAs, oleic acid is the more important MUFA, is the predominant fatty acid in human pancreatic extracts (23, 32) and in human pancreatic necrotic collections (6, 7). *In vitro* and laboratory animal studies suggest that oleic acid is associated with local and systemic toxicity (7, 10, 11, 33–35). In addition, in a study by Pironi et al. in patients with parenteral nutrition, the administration of a lipid emulsion based on MUFA produces a higher inflammatory status than in patients using a fish-oil based lipid emulsion (36). In the present study, residing in a region with high MUFA intake was independently associated with local complications and with moderate-to-severe AP in the model without obesity and with moderate-to-severe AP in the model that included obesity. In addition, two studies investigated halogenated fatty acids, a type of specific lipids produced from the oxidation of fatty acids by hypochlorous acid, in humans and in an animal model of AP. The animal model showed that the induction of AP produces an important release of free fatty acids from adipose tissue and also in the release of the chlorohydrins of oleic acid. Only the chlorohydrin of oleic acid was present in plasma (10). In humans, we found that oleic acid chlorohydrin was an excellent early marker of moderate-to-severe disease (11).

This study has several strengths, including the use of multicenter data and nationwide prospective data from patients with AP and the robust design and development of the ANIBES study. There are also some limitations: we used indirect data regarding dietary fat intake (regional consumption of fat according to the ANIBES study) instead of obtaining individual dietary data from every patient. It is difficult to conduct a prospective study that involves a similar sample of patients with detailed individual dietary information, and the lack of validated food questionnaires for the analysis of dietary fat and the different sources that are used in different countries make it difficult to perform an international study. Furthermore, dietary patterns are difficult to address in acutely ill patients, as this usually involves self-registry of food intake. Finally, a diet questionnaire is time-consuming, decreasing the feasibility of such a study due to the high number of patients required to reproduce our findings. However, we encourage the development of a multicenter prospective cohort study, which would provide more insights into the influence of lipids on AP. Besides, more nutritional data should be analyzed in further studies as PUFA, including the omega-6/omega-3 ratio that can be crucial in inflammatory processes. This is a limitation of the study although future studies by our group will include the omega-6/omega-3 ratio in order to have a more complete and global vision of the process. On the other hand, the *de novo* lipogenesis index (the synthesis of new fatty acids from non-lipid sources) will be evaluated in further studies by our research team. This index has a known correlation with metabolic disorders such obesity and type 2 diabetes and with inflammatory processes like moderate-to-severe AP. Finally, the influence of dietary fat patterns with possible similar pathophysiology could be studied in other severe diseases like a sepsis.

In conclusion, differences in regional dietary fat patterns seem to be associated with different outcomes of AP. Dietary fat patterns could represent a significant pre-morbid factor that determines the severity of AP. Moreover, UFAs, and particularly MUFAs, seem to be important mediators of the pathogenesis of the severity of AP.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité Ético de Investigación con Medicamentos del Hospital General Universitario de Alicante (PI2018-102). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EM: conception, design, acquisition of data, analysis and interpretation of data, article drafting. GG-R: article drafting, acquisition of data, analysis and interpretation of data, and critical review for important intellectual content. GV-M: acquisition of data, analysis and interpretation of data, article drafting, and critical review for important intellectual content. ÁL and DC: article drafting and critical review for important intellectual content. ÁF, NB-L, JC, MB-B, AA-A, PL, MU-C, MS-C, JL-N, RG-F, CG-O, RI-U, CR-A, JS, MR-P, AM-Á, EO, MM, FB, JR-P, and SG-S: acquisition of data and critical review for important intellectual content. All authors gave final approval of the version to be published.

FUNDING

GG-R was supported by grant from the Instituto de Salud Carlos III and Instituto de Investigación Sanitaria (IIS) Aragón [Río Hortega grant CM17/00145].

ACKNOWLEDGMENTS

The results of this study were partially presented as a poster presentation at the 50th meeting of the European Pancreatic Club celebrated in Berlin from June 13 to 16, 2018.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00126/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Capítulo 4: Hacia un manejo de la pancreatitis aguda personalizado y basado en la evidencia

Se trata de una revisión en la que se resume la evidencia actual sobre diferentes aspectos importantes en el manejo de la PA, concretamente el diagnóstico, etiología, historia natural y tratamiento precoz de la PA. En el apartado de diagnóstico se especifica cuáles son los síntomas característicos de la PA, los test en sangre y orina y las pruebas de imagen para el diagnóstico de la PA. En cuanto a la historia natural, se explica las fases de la PA, las complicaciones locales, las definiciones de FO y las clasificaciones de gravedad. En lo referente al tratamiento precoz de la PA, se sintetiza la evidencia disponible en cuanto a fluidoterapia, soporte nutricional, antibioterapia, analgesia y realización de CPRE. Dicha revisión se construye a raíz de un caso clínico breve, y proponemos en el apartado final las áreas de incertidumbre en la PA sobre las que se deberá trabajar en los próximos años.

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

Review Article

United European Gastroenterology Journal
0(0) 1–7

DOI: 10.1177/2050640620903225
journals.sagepub.com/home/ueg
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Towards evidence-based and personalised care of acute pancreatitis

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Abstract

Acute pancreatitis is a heterogeneous illness. Most patients experience a mild course of disease, but one third will develop local complications and/or organ failure associated with increased morbidity and risk of mortality. Diagnosis of acute pancreatitis is based on typical epigastric pain, elevation of serum lipase or amylase levels, and/or characteristic findings on imaging. Personalised management is needed in patients with acute pancreatitis. Currently, analgesia, Ringer's lactate solution-based goal-directed fluid resuscitation and early oral refeeding providing enteral nutrition if not tolerated are the cornerstones for early management. Prophylactic antibiotics or endoscopic retrograde cholangiopancreatography in the absence of cholangitis are considered to be futile. Future clinical trials should address optimal fluid resuscitation, the early administration of anti-inflammatory drugs and the exact role of nutritional support in severe acute pancreatitis. Here, we present a patient case and review the diagnosis, treatment and prognosis of acute pancreatitis.

Keywords

Acute pancreatitis, amylase, revised Atlanta classification, Ringer's lactate solution, enteral nutrition, antibiotics

Received: 13 November 2019; accepted: 2 January 2020

Brief clinical case

A 45-year-old male patient presented to the emergency room with acute-onset epigastric pain and vomiting. The patient was an active smoker and consumed up to one unit of alcohol per day. The patient reported no chronic diseases or previous surgical interventions.

How to diagnose acute pancreatitis

According to the revised Atlanta classification (RAC), for the diagnosis of acute pancreatitis (AP), the patient should meet at least two of the following three criteria:[1] typical abdominal pain (acute onset of epigastric pain often radiating to the back), serum lipase or amylase at least three times the upper limit of normal (ULN) and characteristic findings of AP on imaging.

Symptoms

The cardinal symptom of AP is sudden-onset acute epigastric abdominal pain, often radiating to the back. Nausea and vomiting are very frequent.

Blood and urine tests

Serum amylase and/or lipase have been used to diagnose AP for more than seven decades.[2] The two major sources of serum amylase are the pancreas and the salivary glands; the specific isoforms of pancreatic amylase can be measured in the blood, and some laboratories only determine those isoforms to rule out the influence of salivary amylase. Its serum activity starts to rise within six hours after the onset of AP, peaks at 48 hours and normalises in five to seven days.[3] Lipase comes almost exclusively from the pancreas and so it is considered to be more specific for AP.[3] It rises after four to eight hours, peaks at 24 hours and remains at high levels longer than amylase (8–14 days).[3]

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Regarding urine markers, we can measure urinary amylase or perform the quick trypsinogen-2 dipstick test.[3] Both have a good sensitivity and specificity. However, the trysinogen-2 dipstick test has a limited availability.[4] Urine markers can be more useful when there is high diagnostic suspicion of AP and blood amylase or lipase normal levels, for example, in cases of hypertriglyceridaemia.[5] Interestingly, there is no evidence of an analytical test that is more accurate than other tests.[3] Repeated measures of pancreatic enzyme levels in blood or urine are not useful for predicting severity or monitoring the disease course.

Other causes of acute abdominal pain and inflammation are associated with increased amylasaemia or lipasaemia, including acute cholecystitis, cholangitis, perforation, acute mesenteric ischaemia or gynaecological problems. Inflammatory diarrhoea and diabetic ketoacidosis are other causes of acute increases of pancreatic enzymes in the blood and urine. These alternative diagnoses are usually associated with atypical signs or symptoms. In this scenario, imaging is needed.

Imaging

Imaging is needed for three purposes: (a) early in the course of disease for differential diagnosis in cases of atypical signs or symptoms, (b) to diagnose local complications of AP and (c) to determine the aetiology of AP.

Differential diagnosis. Imaging is not needed to diagnose AP in patients with typical features of AP and elevated amylase or lipase blood levels higher than three times the ULN.[1] In cases of atypical signs or symptoms (e.g. high-grade fever, chills, peritoneal signs, diarrhoea, pain in central or lower quadrants), a contrast-enhanced computed tomography scan (CECT) is particularly useful to confirm AP. However, abdominal ultrasonography has higher sensitivity and specificity for diagnosing acute cholecystitis compared to CECT.[6]

Diagnosis of local complications. During admission, CECT and abdominal magnetic resonance imaging (MRI) are used to evaluate the severity of pancreatitis by detecting the presence of local complications.[7] These techniques should not be performed before the first 72 hours, as they may underestimate the severity of AP,[8] and should only be performed when local complications are suspected (predicted severe disease, persistent pain, persistent systemic inflammatory response syndrome (SIRS), inability to resume oral feeding or early satiety, presence of an abdominal mass, etc...).

Determination of aetiology of AP. As a first step to guide the aetiological work-up of AP properly, it is essential to have a good medical history, a complete blood test that includes the hepatic and lipid profiles as well as calcium levels and an abdominal ultrasound.[8] After recovery, it is recommended that triglyceride and calcium levels in the blood are measured again in patients with unknown aetiology, as alcohol is a cause of hypertriglyceridaemia, and necrosis may be associated with hypocalcaemia during the course of disease. The most frequent causes of pancreatitis are listed in Table 1. Endoscopic ultrasound is particularly useful in cases of unknown aetiology after the first step. Besides, MRI or endoscopic ultrasonography can be used to rule out choledocholithiasis in gallstone-related AP.

Natural history

About two-thirds of AP patients have a mild course of disease with a quick recovery. However, one third experience disease progression, with the development of local complications and/or organ failure (OF). Two phases are apparent in moderate-to-severe AP: an early phase during the first week and a late phase thereafter.[1] In the early phase, the release of pro-inflammatory agents due to local pancreatic and peri-pancreatic tissue damage may result in the development of SIRS. Uncontrolled inflammation is associated with OF. The development of local complications (collections, necrosis) is linked to fluid sequestration during the early phase but, most importantly, has consequences in the late phase, in which those local complications can be associated with symptoms and infection.

Local complications

There are two types of AP: interstitial and necrotising AP. In interstitial AP, the pancreas is enlarged due to inflammatory oedema. Some patients with interstitial AP may develop acute peri-pancreatic fluid collections (APFC), which are early (<4 weeks) homogeneous collections (without necrotic debris) with no defined wall. Most APFC are reabsorbed; those persisting more than four weeks develop a defined wall and are called pseudocysts.[1]

Necrotising AP is characterised by the presence of pancreatic or/and peri-pancreatic necrosis. In the first four weeks, these collections lack a defined wall and are called acute necrotic collections (ANC). ANC are heterogeneous due to the presence of fluid and necrotic debris inside. ANC persisting for more than four weeks develop a defined wall and are known then as walled-off necrosis.[1]

All local complications increase morbidity in AP, but only an increase of mortality occurs if persistent OF is present.[9] The infection of pancreatic or

Table 1. Aetiology.

Pathogenesis	Aetiology
Obstruction	• Gallstones, gallbladder polyps, gallbladder cholesterolosis • Pancreatic and peri-ampullary tumours (especially IPMNs) • Pancreatic duct post-necrotic stenosis • Sphincter of Oddi dysfunction • Pancreas divisum (controversial) • Anomalous pancreaticobiliary junction • Duodenal obstruction/diverticulum/duplication cyst • Choledochocele/choledochal cyst • Parasites (e.g. *Ascaris lumbricoides*)
Toxicity, allergy	• Alcohol, smoking • Scorpion venom • Drugs (e.g. valproic acid, azathioprine, calcium channel blockers, diclofenac, didanosine, angiotensin converting enzyme inhibitor, etc.)
Metabolic disease	• Hypertriglyceridaemia • Hypercalcaemia (primary hyperparathyroidism)
Infection	• Hepatitis A, B and E virus • Cytomegalovirus • Coxsackievirus • Other, including mumps, HSV, HIV, *Legionella*, *Mycoplasma*, *Salmonella*, *Leptospira*, *Aspergillus*, *Toxoplasma*, *Cryptosporidium*
Iatrogenic	• After ERCP, pancreatic biopsy, percutaneous trans-hepatic cholangiography, surgery
Genetic	• Mutations of *PRSS1*, *CFTR*, *SPINK1*, *CTRC*, *CPA1* and *CEL*
Other	• Autoimmune pancreatitis • Kidney transplantation • Peritoneal dialysis, haemodialysis • Vasculitis • Ischaemia • Trauma

From: *Fast Facts: Acute and Recurrent Pancreatitis*, by Enrique de-Madaria and Matthias Löhr. Karger Publishers Limited, in press. ERCP: endoscopic retrograde cholangiopancreatography; HIV: human immunodeficiency virus; HSV: herpes simplex virus; IPMN: intraductal papillary mucinous neoplasm. ERCP: endoscopic retrograde cholangiopancreatography; HIV: human immunodeficiency virus; HSV: herpes simplex virus; IPMN: intra-ductal papillary mucinous neoplasm.

peri-pancreatic necrosis is particularly associated with worse outcomes.

OF

OF is defined in AP, according to the RAC, by the modified Marshall scoring system.[1,10] OF is present if the patient has two or more points in the modified Marshall score, namely: respiratory (PaO2/FiO2 $\leq$ 300); renal (serum creatinine $\geq$1.9 mg/dL) and/or cardiovascular (systolic blood pressure $<$ 90 mmHg not responsive to fluid resuscitation).

OF can be transient (up to 48 hours) or persistent (lasting for more than 48 hours) and single or multiple (if more than one system is affected). Any OF increases morbidity and mortality, but the risk of mortality is greatly increased in persistent OF and/or multiple OF (approximately 50% mortality in both types of OF according to prospective data).[9]

Classification of severity

The RAC, published in 2012[1], updated the classic Atlanta classification (1993).[11] Based on the natural history of complications in AP, RAC defines three categories: mild, moderately severe and severe (Table 2). The mild category, which includes patients lacking local or systemic complications or OF, results in low morbidity and null mortality. Moderately severe AP is characterised by local complications and/or systemic complications (exacerbation of pre-existing co-morbidity) and/or transient OF, and is associated with increased morbidity but low mortality. Finally, the severe category is defined by persistent OF, and is linked to maximum morbidity and a high risk of mortality.[9] The early prediction of severity in AP is not fully addressed in this review, but briefly, advanced age, patients with obesity, co-morbidity, increased serum blood urea nitrogen and/or

Table 2. Categories of severity according to the revised Atlanta classification.[1,9]

Category	Definition	Consequences
Mild	No complications, no OF	Mild course of disease
Moderately severe	Local complications and/or systemic complications[a] and/or transient (≤48 hours) OF	Morbidity but low risk of mortality
Severe	Persistent (>48 hours) OF	Maximum morbidity and high risk of mortality

[a]Systemic complication: exacerbation of pre-existing co-morbidity.
OF: organ failure.

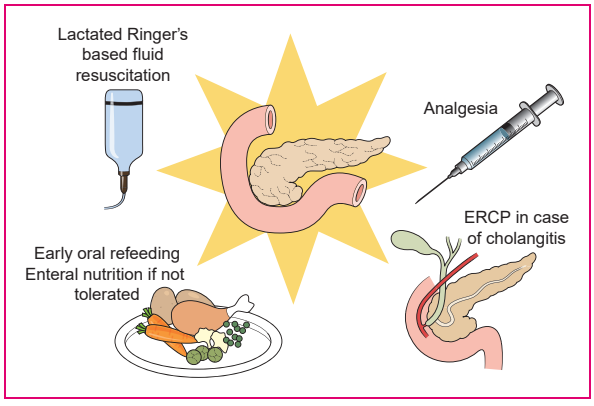

Figure 1. Early management of acute pancreatitis.

haematocrit, patients with SIRS (particularly if lasting for more than two days) have a higher probability of adverse outcomes.[9,12] Several scores (e.g. APACHE-II, BISAP and Ranson score) have been developed to try to increase the accuracy, but in general, all of them are associated with a high negative but low positive predictive value.[13]

Current early management of AP

The cornerstones of the early management of AP are shown in Figure 1.

Fluid resuscitation

Hypovolaemia is frequent in AP for several reasons. First, AP is associated with increased vascular permeability with extravasation of fluids into tissues (vascular leak syndrome), which together with local complications and paralytic ileus produces fluid sequestration. In addition, there is an increase in fluid loss due to vomiting, sweating (due to increased body temperature), tachypnoea associated with SIRS, and decreased oral intake of liquids. Severe hypovolaemia may result in decreased organ perfusion that can be countered with adequate fluid resuscitation. However, aggressive fluid resuscitation in patients without hypovolaemia may result in pulmonary oedema and increased intra-abdominal pressure, resulting in abdominal compartment syndrome.

Volume. The optimal volume rate in AP is controversial, and the few available trials have provided conflicting results. In 2009[14] and 2010,[15] two randomised clinical trials (RCTs) on severe AP from the same group showed that patients assigned to aggressive fluid therapy presented worse outcomes (higher morbidity and mortality). These were open-label single-centre trials with some flaws. A recent RCT focused on patients with predicted mild AP compared to aggressive versus moderate fluid resuscitation based on Ringer's lactate (RL) solution.[16] The primary outcome was 'clinical improvement within 36 hours' that required a decrease in haematocrit, blood urea nitrogen and creatinine levels, decreased pain, and tolerance to oral diet. Patients under aggressive fluid resuscitation showed a higher rate of that primary outcome. The definition of 'clinical improvement' has been criticised for relying too much on haemodilution, which is not a direct marker of a good disease course, and it is clear that patients receiving aggressive fluid resuscitation will have quicker haemodilution.[17] Well-designed RCTs are needed. Thus, the evidence of recommendations in the guidelines is weak. International Association of Pancreatology/American Pancreatic Association (IPA/APA)[8] and recent American Gastroenterological Association guidelines[18] recommend goal-directed therapy for fluid resuscitation in AP with low-quality evidence.

Type of fluid. RL solution is recommended for fluid resuscitation in AP, since it is associated with decreased inflammation. In an open-label[19] and in a triple-blind RCT[20] with 40 patients each, RL solution decreased the rate of SIRS and C-reactive protein (CRP) blood levels compared to normal saline. Therefore, IAP/APA[8] and American College of Gastroenterology guidelines[21] recommend RL solution as resuscitation fluid in AP. However, SIRS and CRP are surrogate markers of severity, and new RCTs are required that focus on more important clinical outcomes such as OF, local complications or mortality.[18]

Oral refeeding and nutritional support

Intra-pancreatic-activated trypsin is a key step in the pathophysiology of AP. Because food stimulates the secretion of trypsinogen, the inactive precursor of trypsin, it was previously believed that 'pancreatic rest' improved outcomes (patients were nil by mouth until complete recovery, with or without parenteral feeding). However, several studies have subsequently challenged that belief.

Nutrition in mild AP. RCTs have shown that in mild AP, early oral refeeding is safe and results in a shorter hospital stay.[22,23] Furthermore, starting with clear liquids with a step-up progression to solid diet is not necessary, and initiation of refeeding with a fully solid diet is well tolerated and also results in a shorter hospital stay.[22]

Nutrition in moderate to severe AP. In a multi-centre RCT, in patients with predicted severe AP, early naso-jejunal feeding within 24 hours did not show better outcomes compared to on-demand enteral nutrition (used only in patients without tolerance to oral diet on day 4).[24] Therefore, in moderate to severe AP, an attempt at oral refeeding can be done, reserving tube feeding if oral diet is not tolerated after three to four days. In patients who cannot tolerate oral feeding, nutritional support with enteral nutrition is clearly superior to total parenteral nutrition (TPN). RCTs and meta-analysis have demonstrated a decrease in infection complications, the need for operative interventions, OF and mortality with enteral nutrition compared to TPN.[25] Hence, in this setting, guidelines for AP strongly recommend enteral nutrition.[8,18,21] Regarding the route of enteral feeding, three RCTs and two meta-analyses (although with some methodological flaws) compared naso-jejunal versus nasogastric tube feeding, and showed no differences in mortality, need for surgery or abdominal pain.[26] However, in the presence of gastric outlet obstruction, a naso-jejunal tube is preferred.

Antibiotics

Antibiotic treatment is not recommended in AP unless pancreatic necrosis infection or other infection is present or highly suspected. Early open-label RCTs showed a benefit of prophylactic antibiotics for the prevention of pancreatic necrosis infection. Nevertheless, these studies had methodological flaws. More recent better-designed double-blind RCTs and meta-analysis of RCTs did not demonstrate a reduction in pancreatic necrosis infection or mortality with prophylactic antibiotics.[18] Consequently, the current AP guidelines do not recommend the use of prophylaxis antibiotics in AP.[8,18,21]

Early endoscopic retrograde cholangiopancreatography

A meta-analysis of RCTs comparing early endoscopic retrograde cholangiopancreatography (ERCP) versus conservative management in AP showed no benefits for early ERCP in the absence of acute cholangitis.[27] The latter is the only widely accepted indication for urgent exploration of the biliary tree.[18]

Similar to the case of prophylactic antibiotics, earlier studies suggested the reduction of complications, biliary sepsis and hospital stay with ERCP within 24–72 hours. However, these benefits were not confirmed in later well-designed RCTs. A recent RCT from the Dutch pancreatitis study group addressing this scenario is expected to be published soon. The preliminary analysis published as an abstract in the *United European Gastroenterology Journal* also suggests that early ERCP is not associated with better outcomes.[28]

Analgesia

Although some RCTs have compared different analgesics in AP, most of them only included a few patients and had low methodological quality.[29] Therefore, there is no firm consensus on which drug and which route of administration are preferable in AP. A systematic review concluded that opioids might reduce the need for supplementary analgesics without increasing the adverse effects.[30] Classic non-steroidal anti-inflammatory drugs (NSAIDs) and metamizole can be used to treat AP pain, although their adverse effects (gastrointestinal damage and renal impairment with NSAIDs and neutropenia with metamizole) must be considered. Epidural analgesia may be an alternative in patients with intense pain due to AP.

Final outcome and areas of uncertainty

The patient had SIRS at presentation. Blood tests showed increased blood amylase levels of 3500 IU/L (ULN 100 IU/L) and haematocrit of 51%. The patient needed aggressive fluid resuscitation to maintain an adequate urine output (>0.5 mL/kg/h), but oral feeding was effectively started on day 3. An abdominal ultrasonography showed cholelithiasis. A CT scan was performed on day 4 showing an acute peri-pancreatic fluid collection. A follow-up outpatient ultrasonography showed reabsorption of the collection, and so cholecystectomy was performed on day 30.

While several RCTs have clarified the treatment of late complications,[31,32] many questions regarding the early management of AP remain. Future studies should address specific drugs aimed at improving inflammation at an early stage, and identifying the

optimal volume and type of fluid resuscitation, role of nutritional support (routes, different composition of nutritional supplements), new ways to prevent pancreatic necrosis infection (selective gut decontamination) and optimal analgesic drugs.

Acknowledgements

We thank S. Karger Publishers Limited for their permission to include Table 1 in this review.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Enrique de-Madaria reports receiving consulting fees from Takeda Pharmaceutical Company Limited, fees for serving on a data and safety monitoring board from Kowa Research Institute, and travel support and lecture fees from Abbott and Mylan.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: G.G.-R. was supported by a grant from the Instituto de Salud Carlos III and the Instituto de Investigación Sanitaria (IIS) Aragón (Río Hortega grant CM17/00145).

Ethics approval

Not applicable.

Informed consent

Not applicable.

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Discusión general y conclusiones

Capítulo 1: Determinantes de gravedad en pancreatitis aguda

La incidencia de la PA ha aumentado considerablemente en las últimas décadas hasta convertirse en una de las enfermedades digestivas más frecuentes [1, 2]. Por lo tanto, son necesarios esfuerzos por parte de la comunidad científica para conocer mejor los mecanismos fisiopatológicos de la PA y para realizar avances en cuanto a sus factores pronósticos, clasificación, diagnóstico y tratamiento.

Una clasificación apropiada es aquella basada en los conocimientos actuales en cuanto a los determinantes y marcadores asociados a la evolución de la enfermedad. Una correcta estratificación de la gravedad es necesaria para las comparaciones de datos intra- e inter-institucionales, para el desarrollo de estrategias terapéuticas y en el campo de la investigación. Así, el objetivo del primer capítulo de esta tesis doctoral es validar las últimas clasificaciones de gravedad de la PA y determinar las características de la enfermedad asociadas a una peor evolución.

Como se ha descrito en el apartado previo *1.2 Resultados*, en nuestro estudio tanto las clasifiaciones RAC como la DBC fueron superiores a la antigua clasificación de Atlanta (AC) estratificando a los pacientes en grupos homogéneos. Sin embargo, no encontramos diferencias significativas entre ambas clasificaciones. El FO persistente fue el determinante de morbilidad y mortalidad más relevante y decisivo por lo que debe ser parte esencial de cualquier clasificación de PA. Por otra parte, en nuestro análisis todas las complicaciones locales incluidas las colecciones agudas no necróticas se asociaron a una peor evolución de la PA. Estos resultados refuerzan la RAC ya que en esta clasificación los pacientes con cualquier complicación local pero sin FO persistente son clasificados como moderadamente graves. En cambio, la DBC sólo considera la necrosis pancreática como determinante de gravedad y sin embargo de acuerdo con nuestros resultados las otras complicaciones locales también se asocian independientemente a una peor evolución.

En el trascurso de la PA la necrosis pancreática se puede infectar, lo que tiene consecuencias negativas en el curso clínico de los pacientes. Un metaanálisis publicado en 2010 mostró que la coexistencia de infección de la necrosis pancreática con FO resultaba en una mayor mortalidad en comparación con el FO sin infección [3]. En base a este metaanálisis la DBC estableció una categoría grave para los pacientes que presentan infección de la necrosis o FO persistente, y una categoría más grave (crítica) para los pacientes en que coexiste la infección con el FO persistente. La RAC sin embargo no tiene en consideración esta combinación. Los resultados de nuestro estudio muestran que, si en el análisis multivariante se incluye el FO persistente, la infección de la necrosis pancreática se asocia a una mayor morbilidad pero no a una mayor mortalidad. Por tanto, este hallazgo respalda una vez más a la RAC frente a la DBC.

Por último, el fallo multiorgánico no se incluye ni en la RAC ni en la DBC. En nuestro análisis el fallo multiorgánico fue independientemente asociado a una mayor morbilidad y mortalidad en comparación con el FO simple por lo que debería tenerse en cuenta en las clasificaciones de gravedad de la PA.

En base a nuestros resultados proponemos una modificación de la RAC para un mayor ajuste a las características que condicionan la gravedad en la PA. Esta modificación consistiría en subdividir la categoría moderadamente grave en dos grupos. Un primer grupo con morbilidad pero baja que incluiría al FO transitorio, la exacerbación de la comorbilidad previa, las colecciones agudas no necróticas y la necrosis pancreática o peri-pancreática aisladas. Y un segundo grupo con alta morbilidad en el que se incorporarían los pacientes con infección de la necrosis pancreática, o con combinación de la necrosis pancreática y peri-pancreática. Por último, en la categoría grave además de los pacientes con FO persistente se debería incluir los pacientes con fallo multiorgánico. Esta nueva propuesta de clasificación de gravedad se resume en la *Tabla 6*.

Tabla 6. Propuesta de modificación de la Clasificación revisada de Atlanta.

Categoría	Definición	Morbilidad/Mortalidad
Leve	No complicaciones ni FO	Muy baja / Nula
Moderadamente grave	Grado 1: FO transitorio, exacerbación comorbilidad, colecciones agudas no necróticas, necrosis aislada*	Baja / Baja
	Grado 2: infección de la necrosis, combinación necrosis pancreática y peripancreática	Alta / Baja
Grave	FO persistente y/o multiorgánico	Alta / Alta

*Necrosis pancreática o peri-pancreática.

FO: Fallo orgánico.

Este estudio tiene fortalezas importantes como su naturaleza prospectiva y multicéntrica y su gran número de pacientes incluidos. Estudios previos fueron retrospectivos o con inclusión de pocos centros lo que limitaba su validez externa. Sin embargo, este estudio también tiene algunas limitaciones. Las imágenes de los TAC para determinar complicaciones locales no fueron revisadas de manera central por un único radiólogo sino por los radiólogos de cada centro. Además, a los pacientes con curso leve de la PA no se les realizó TAC y se consideró que no presentaban complicaciones locales lo que pudo dejar sin detectar alguna complicación local. Sin embargo, estas dos limitaciones son aspectos que reflejan la práctica clínica diaria de los pacientes con PA y la no realización de TAC en pacientes con curso leve se ajusta a las recomendaciones de las principales guías clínicas de PA.

Por todo lo anterior a modo de síntesis final se pueden extraer las siguientes conclusiones que enumeramos a continuación:

- La RAC y la DBC son clasificaciones superiores a la AC.
- El FO persistente es el mayor determinante de gravedad en PA.
- Cualquier complicación local de la PA se asocia a una peor evolución clínica.

- La presencia de infección de la necrosis se relaciona con una mayor gravedad por aumento de la morbilidad, pero no aumenta la mortalidad si el FO persistente no está presente.

Capítulo 2: Influencia de la edad, el índice de masa corporal y la comorbilidad en la evolución clínica de la pancreatitis aguda: un estudio prospectivo multicéntrico a escala nacional.

En una enfermedad heterogénea como la PA existen pacientes con una evolución clínica diferente, desde pacientes con un curso clínico leve hasta pacientes con una morbi-mortalidad muy elevada. En este contexto, pronosticar la gravedad de los pacientes puede aportar una serie de beneficios. En primer lugar, los pacientes identificados como potencialmente graves pueden ser controlados más estrechamente y si a lo largo de su evolución desarrollan FO se podría diagnosticar y tratar de una forma más temprana. Además, algunos ensayos clínicos que testan posibles medicamentos para el tratamiento de la PA sólo permiten incluir pacientes con pronóstico de gravedad. Por último, predecir la gravedad de los pacientes es útil para seleccionar que pacientes se pueden beneficiar de la realización de un TAC para detectar complicaciones locales.

En una multitud de estudios la comorbilidad ha demostrado ser un importante factor de riesgo para una peor evolución de procesos agudos tanto en una serie de diagnósticos médicos individuales como en pacientes no seleccionados que requieren hospitalización desde Urgencias [4, 5]. Teniendo en cuenta la importancia de la comorbilidad en la predicción de la gravedad en otras enfermedades, llama la atención la escasez de estudios en la literatura sobre la influencia de la comorbilidad en la PA. Aparte de la limitada presencia de algunas comorbilidades incluidas en el sistema de puntuación predictivo *APACHE II (Acute Physiology and Chronic Health Evaluation II)*, el resto de modelos clínicos predictivos de gravedad de PA no incluyen la comorbilidad [6]. En un estudio publicado hace más de una década, las comorbilidades incluidas en el Índice de Comorbilidad de Charlson se asociaron con mortalidad y desarrollo de fallo multiorgánico dentro de las dos primeras semanas de hospitalización por PA [7]. Sin embargo, este estudio tenía importantes limitaciones como su naturaleza retrospectiva, el empleo de una base administrativa con diagnósticos basados en la ICD 9

(*International Classification of Diseases, Ninth Revision*) y la ausencia de utilización de análisis de supervivencia. La naturaleza de nuestro estudio prospectivo y multicéntrico con 1655 pacientes es más robusta y en él se demuestra que la comorbilidad es un predictor independiente de mortalidad intrahospitalaria a los 30 días y de FO persistente. Además, incrementos en la puntuación de comorbilidad se relacionaron significativamente con aumento de la mortalidad a los 30 días y aumento del FO persistente.

La obesidad está asociada a un aumento de la grasa intrapancreática y peripancreática. Cuando se produce una PA la lipasa pancreática induce lipólisis de los adipocitos de la grasa intra y peripancreática produciendo la liberación de ácidos grasos insaturados que provocan lipotoxicidad local que podría contribuir tanto al desarrollo de necrosis pancreática como de toxicidad sistémica que en caso de ser intensa podría conducir a la aparición de FO [8, 9]. Así, la obesidad ha sido asociada a una mayor frecuencia de complicaciones locales, FO y mortalidad de la PA en numerosos estudios y metaanálisis [10, 11]. Pero la gran mayoría de estos estudios no tiene en cuenta ni incluyen en sus análisis multivariantes las diferentes comorbilidades, y en los pocos estudios en los que se tienen en cuenta se incluyeron muy pocas comorbilidades [12, 13]. En nuestro estudio incluimos en el análisis multivariante multitud de comorbilidades según el Índice de Comorbilidad de Charlson (ampliamente validado) y mostramos que la obesidad se asocia de manera independiente a un aumento de la mortalidad a los 30 días y a un aumento de FO persistente. Por otra parte, algunos estudios con limitaciones metodológicas sugirieron la presencia de la "paradoja de la obesidad" en la evolución de la PA. Según esta hipótesis los pacientes con sobrepeso tendrían una mejor evolución con menor mortalidad que los pacientes con normopeso o bajo índice de masa corporal [14]. En nuestro estudio con una metodología y análisis más riguroso demostramos que el sobrepeso también está relacionado con un aumento de la mortalidad a los 30 días en PA.

La edad avanzada ha sido ampliamente estudiada como marcador de gravedad en PA y ha sido incorporada a numerosos sistemas clínicos pronósticos como el *APACHE-II score* [15], el sistema de *Ranson*, el sistema *BISAP (the bedside index for severity in*

acute pancreatitis) [16] y en el sistema de predicción de gravedad japonés [17]. Una edad con un rango de mayor de 45 años hasta mayor de 70 años se asoció a una peor evolución de la PA. En nuestro estudio, contrariamente a los estudios anteriores publicados, sólo la edad avanzada extrema (mayor de 85 años) se asoció a un aumento de la mortalidad en PA. La explicación más lógica de nuestros hallazgos es que la edad avanzada se asocia a un gran número de comorbilidades y consecuentemente después de ajustar el análisis con las diferentes comorbilidades gran parte de la relación entre edad y peor pronóstico se pierde. Así, las comorbilidades de los pacientes tendrían un mayor peso en el pronóstico de la enfermedad que una simple cifra de edad que en muchas ocasiones no refleja el estado de salud de un paciente. Es más importante la edad biológica de un paciente que la edad cronológica [18].

Por último, la comorbilidad y la obesidad no se asociaron en nuestro análisis a un aumento de la estancia hospitalaria que se considera marcador de morbilidad, pero hay que destacar que el análisis multivariante para la estancia hospitalaria incluía el FO. Así la comorbilidad y la obesidad podrían aumentar la estancia hospitalaria en los casos que se asociaran al desarrollo de FO, pero en ausencia de FO no aumentarían la estancia hospitalaria. Este hallazgo podría tener consecuencias en la clasificación de gravedad RAC ya que en ésta la exacerbación de una comorbilidad previa se clasifica como PA moderadamente grave lo cual puede ser redundante puesto que la exacerbación de una comorbilidad previa produciría aumento de la morbilidad en la medida que produjera FO el cual ya es un componente clave en la RAC.

En conclusión, en nuestro estudio mostramos que la comorbilidad y la obesidad se asocian a un aumento de mortalidad a los 30 días y desarrollo de FO persistente por lo que deberían utilizarse en la estratificación de riesgo de los pacientes con PA y deberían incluirse en los sistemas clínicos de pronóstico de gravedad en PA. Además, después de ajustar por la presencia de FO, la comorbilidad y la obesidad no se asociaron a aumento de la estancia hospitalaria por lo que la inclusión de “exacerbación de comorbilidad previa” en la categoría moderadamente grave de la RAC puede ser redundante.

Capítulo 3: Patrones de consumo de grasa en la dieta y curso clínico de la pancreatitis aguda en España.

Análisis post mortem de tejidos de pacientes obesos han mostrado que los UFAs son los ácidos grasos que predominan en el páncreas, mientras que la proporción de SFAs es más baja [19, 20]. Además, los UFAs son los ácidos grasos más frecuentes (constituyen hasta el 70-75%) en las colecciones pancreáticas necróticas [8, 9, 21, 22]. Por otra parte, el grupo de investigación del doctor *V.P. Singh* ha realizado en la última década experimentos *in vitro* y en modelos animales con ratas que sugieren que los UFAs están asociados a inflamación y necrosis celular mientras que los SFAs no son tan dañinos. Estos experimentos muestran que los UFAs son consecuencia de la lipólisis de la grasa visceral pancreática realizada por la enzima pancreática lipasa, que a nivel local los UFAs producen necrosis de las células acinares pancreáticas, y que la liberación incontrolada de los UFAs produce un aumento de sus niveles sanguíneos llegando a nivel renal donde producen apoptosis de las células renales tubulares (provocando FO renal) y a nivel pulmonar donde dañan las células alveolares produciendo FO pulmonar [8, 9, 22, 23].

Estudios en animales han mostrado que la composición de la grasa de la dieta puede afectar a la proporción de los diferentes tipos de lípidos presentes en la grasa corporal. Ratones con una dieta rica en ácido oleico y pobre en ácido linoleico presentaron estas diferencias en sus tejidos adiposos y en la composición de la grasa pancreática [19]. Además, estudios en humanos mostraron que la diferente proporción de ácidos grasos del tejido adiposo y el plasma reflejan, al menos en parte, las diferencias en el tipo de grasa ingerida en la dieta [24, 25].

Teniendo en cuenta lo anterior, la hipótesis del estudio fue que las diferencias regionales en el consumo de diferentes tipos de grasa podrían condicionar una diferente evolución de la PA. Además, quisimos investigar si este efecto en la evolución de la PA sería independiente de la presencia de obesidad. Por tanto, comparamos la evolución de la PA en los pacientes de regiones de España con diferente ingesta de grasa en la dieta. Según nuestro conocimiento, este es el primer estudio de este tipo realizado en España o en otros países. Describimos que los pacientes con PA provenientes de regiones de España

con un alto consumo de UFAs tuvieron significativamente más complicaciones locales, FO persistente, mortalidad y PA moderada-grave. Al incluir la obesidad en el análisis multivariante se mantuvo la asociación significativa con un aumento de FO persistente que es el principal determinante de gravedad en PA. Por tanto, estos resultados sugieren que un alto consumo de UFAs podría ser un factor determinante de gravedad en PA.

En cuanto a los diferentes tipos de UFAs, el ácido oleico es el MUFAs más importante y el ácido graso predominante en el páncreas humano [19]. Estudios *in vitro* y en modelos animales han mostrado que el ácido oleico está relacionado con toxicidad local y sistémica [9, 26]. En nuestro estudio, residir en una región con un alto consumo de MUFAs se asoció de forma independiente a mayores complicaciones locales y PA moderada-grave en el modelo multivariante sin obesidad, y a PA moderada-grave en el modelo con obesidad. Estos resultados están en concordancia con otros estudios liderados por el doctor *Daniel Closa* (*Consejo Superior de Investigaciones Científicas*, Barcelona) con la colaboración de nuestro grupo, realizados en animales y humanos con ácidos grasos halogenados (clorhidrinas) que son un tipo específico de lípidos producidos por la oxidación de los ácidos grasos por el ácido hipocloroso. En el modelo animal la inducción de una PA produjo una marcada liberación de clorhidrinas del ácido oleico a plasma [27]. En humanos, otro estudio de nuestro grupo demostró que la clorhidrina del ácido oleico fue un excelente marcador precoz de PA moderada-grave [28].

Este estudio tiene fortalezas como la naturaleza prospectiva y multicéntrica de su parte clínica, incluyendo un gran número de pacientes del proyecto *Atlantis* y la robustez del diseño del estudio *ANIBES* publicado en una de las mejores revistas en el campo de la nutrición (*Nutrients*). Pero también este estudio tiene limitaciones, la principal es que no se emplean datos nutricionales individuales de cada paciente con PA sino datos regionales indirectos (datos nutricionales del estudio *ANIBES*). Es difícil llevar a cabo un estudio prospectivo con un tamaño de muestra tan grande con información nutricional individual y la ausencia de cuestionarios nutricionales validados en los diferentes países hacen que sea complicado realizar un estudio internacional. Además, es difícil obtener información nutricional de pacientes ingresados con una enfermedad

aguda como la PA. En futuros estudios habrá que analizar datos nutricionales adicionales como los PUFAs incluyendo el ratio omega-6/omega-3 que está implicado en procesos inflamatorios y puede ayudar a aportar una visión más completa y global.

En conclusión, las diferencias regionales en España en cuanto al consumo de lípidos parecen estar asociadas a diferente curso clínico de la PA pudiendo constituir un factor determinante de gravedad en PA. Un alto consumo de UFAs y concretamente de MUFAs parecen estar relacionado con una mayor gravedad de la PA.

Capítulo 4: Hacia un manejo de la pancreatitis aguda personalizado y basado en la evidencia

Finalmente, en el último capítulo de esta tesis, presentamos una revisión de la evidencia disponible sobre el diagnóstico, historia natural y tratamiento precoz de la PA. En los últimos años se han producido cambios en el manejo precoz de la PA y es fundamental su conocimiento por parte de los clínicos que atienden esta patología tan frecuente. Existe una conciencia clara por parte de los gastroenterólogos sobre los beneficios de aportar una nutrición enteral precoz en vez de una nutrición parenteral en los pacientes con PA [29]. Sin embargo, la práctica clínica habitual pone de manifiesto que parte de lo clínicos no se adhieren completamente a otras recomendaciones en el manejo de la PA [30] que se explican a continuación.

Tradicionalmente se ha propuesto una fluidoterapia agresiva precoz en los pacientes con PA para prevenir la hipoperfusión orgánica pero la evidencia disponible es escasa presentando la mayoría de los estudios debilidades metodológicas y resultados dispares. Las actuales guías de práctica clínica no aconsejan una fluidoterapia agresiva sino una fluidoterapia basada en objetivos, aunque la evidencia de la recomendación es débil [31]. Son necesarios ensayos clínicos de mayor calidad para tener respuesta a esta incógnita. En cuanto al tipo de fluido, varios ensayos clínicos recientes otorgan al Ringer-Lactato un efecto antiinflamatorio por lo que es el fluido de elección en los pacientes con PA [32]. En lo referente a la profilaxis antibiótica de la infección de la necrosis pancreática, a pesar de ser una práctica clínica extendida en décadas pasadas,

los últimos estudios metodológicamente más potentes que los anteriores y las guías de práctica clínica no aconsejan la profilaxis antibiótica. En cuanto a la realización de la CPRE en PA, la única indicación absoluta es la presencia de colangitis aguda concomitante a la PA [31]. Por último, el mejor régimen de analgesia en PA no está bien establecido pero la utilización de mórficos reduce la necesidad de analgésicos suplementarios sin empeorar la evolución de la PA [33].

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Perspectivas futuras

Tras el término de su tesis doctoral por compendio de publicaciones en pancreatitis aguda el doctorando y sus directores de tesis van a continuar en los próximos años con diferentes líneas de investigación en PA. Las principales líneas de investigación serán:

1. El diseño y validación de una escala de síntomas reportados por los propios pacientes con PA (*patient-reported outcome measure, PROM*).
2. La evaluación de la simvastatina como prevención de PA recurrente mediante un ensayo clínico multicéntrico aleatorizado y triple ciego (*SIMBA trial*).
3. El estudio del efecto de la fluidoterapia agresiva frente a fluidoterapia basada en metas en la fase precoz de la PA mediante un ensayo clínico aleatorizado multicéntrico (*WATERFALL trial*).
4. El estudio prospectivo de la influencia de los diferentes consumos de grasa en la dieta en la evolución de la PA.

En cuanto la primera línea de investigación cabe destacar que en las últimas décadas no se han desarrollado fármacos para el tratamiento específico de la PA por lo que son necesarios nuevos ensayos clínicos. Un inconveniente en los ensayos clínicos de PA es que las variables de resultado *(outcomes o endpoints* en inglés*)* consideradas como clínicamente relevantes (FO, mortalidad…) [1] ocurren de forma infrecuente (FO persistente de acuerdo con el proyecto *Atlantis* ocurre en el 7%, mortalidad en el 4%) por lo que para alcanzar una reducción significativa en estas variables sería necesario incluir miles de pacientes lo que es difícilmente factible. Por ello, una escala *PROM* que se pueda realizar en todos los pacientes con PA y que se correlacionase con las variables de resultado clínicamente relevantes podría ser de gran utilidad en los ensayos clínicos. Además, la escala *PROM* tiene el valor añadido de tener en cuenta los síntomas reportados por los propios pacientes. Por tanto, el objetivo del estudio fue diseñar y validar en una cohorte prospectiva e internacional de pacientes una escala *PROM* en PA. Este estudio ha sido desarrollado en los dos últimos años y ya se disponen de los resultados que han sido publicados recientemente en la prestigiosa revista *Gut* (Primer decil, factor de impacto: 17.9) [2]. El doctorando es coautor de esta publicación.

Se distinguieron dos fases en el estudio, una primera fase de diseño de la escala y una segunda fase de validación. En la primera fase una serie de pacientes recuperados de un episodio de PA y un grupo de profesionales redactó una lista de los síntomas de la PA que consideraron más importantes y molestos. Esta lista de síntomas fue revisada por un panel internacional de expertos en pancreatología dando lugar a la escala final denominada *PAN-PROMISE (Tabla 7).* En la segunda fase se llevó a cabo un estudio prospectivo multicéntrico internacional incluyendo pacientes con PA para validar la escala *PROM*. En total se incluyeron 524 pacientes con PA. La escala obtuvo mayor puntuación en las primeras 24 horas de inicio de los síntomas y puntuaciones más bajas al alta y a los 15 días del alta. Una puntuación más alta a las 48 horas de inicio de los síntomas se asoció significativamente con mayor gravedad de la PA, mayor estancia hospitalaria y con el resto de las variables de resultado [2]. La escala *PAN-PROMISE* mostró buena consistencia, fiabilidad, reproductibilidad y validez empírica por lo que la podemos considerar validada para su utilización como variable de resultado primaria o secundaria en ensayos clínicos con el objetivo de investigar nuevos tratamientos para la PA.

Tabla 7. Escala PAN-PROMISE.

Escala PAN-PROMISE
Dolor, sobre todo localizado en abdomen, pecho o en la espalda
Hinchazón abdominal (sensación de vientre lleno, exceso de gases)
Dificultad para comer; sensación de bloqueo del estómago
Dificultad para ir al baño para hacer de vientre (estreñimiento, excesivo esfuerzo para hacer de vientre)
Náuseas y/o vómitos
Sed
Debilidad, falta de energía, cansancio, dificultad para moverse

Cada ítem es evaluado de 0 a 10 puntos.

En lo referente a la segunda línea de investigación, un 29% de los pacientes con un primer episodio de PA tendrán recidiva de la enfermedad [3]. En algunos pacientes se conoce la causa de la recidiva, por ejemplo, la presencia de colelitiasis, y se pueden realizar tratamientos profilácticos muy efectivos (colecistectomía), pero no es el caso de la PA recurrente (PAR) sin causa aparente, o PAR idiopática, que comprende aproximadamente un 30% de los casos. Además, tras un primer episodio de PA alcohólica y a pesar del consejo de no consumir alcohol, entre un 8 y un 21% de los pacientes presentan recurrencia de la enfermedad [4]. La PAR es causa de extrema

preocupación para los pacientes, ante la ausencia de métodos efectivos de prevención, la morbilidad asociada y las implicaciones sociales, laborales y psicológicas de tener una enfermedad con brotes imprevisibles, en ocasiones graves. Además, supone para los sistemas de salud una importante fuente de gasto sanitario-consumo de recursos.

Por otra parte, en los últimos años se han publicado estudios que apoyan un papel protector de las estatinas para la prevención de la PA. Por ejemplo, en un estudio de cohortes retrospectivo [5] basado en una base de datos que incluía 3,9 millones de usuarios de un seguro privado estadounidense, la incidencia de PA en consumidores de simvastatina fue de 0,80 /100.000 personas-día frente a 1,28 /100.000 personas-día en no consumidores de esta estatina, siendo la ratio de incidencia simvastatina/no simvastatina 0,63 (0,59-0,67), $p<0,0001$. En el análisis multivariante la simvastatina fue un factor independiente asociado a un riesgo menor de PA (hazard ratio 0,29 $p<0,0001$).

Por todo ello, el objetivo del estudio será comparar la incidencia de nuevos episodios de pancreatitis en pacientes con PAR o pancreatitis crónica con reagudizaciones frecuentes bajo tratamiento con simvastatina frente a placebo. Para ello se realizará un ensayo clínico aleatorizado de fase III, multicéntrico, triple ciego, comparando simvastatina frente a placebo (*SIMBA trial*). Dicho ensayo cuenta con financiación suficiente ya que obtuvo una beca de concurrencia competitiva en la convocatoria Acción Estratégica en Salud 2016 del *Instituto de Salud Carlos III* (PI16/01181). Actualmente el ensayo se encuentra en fase de reclutamiento (48 pacientes en junio de 2020). El doctorado participa en dicho ensayo como investigador colaborador en el *Hospital Clínico Universitario Lozano Blesa.*

En cuanto a la tercera línea de investigación, tradicionalmente se ha atribuido a la fluidoterapia agresiva precoz un papel importante en el tratamiento de los pacientes con PA, se ha sugerido que mejoraría el aporte de sangre al tejido pancreático evitando la necrosis del parénquima [6]. En un ensayo clínico abierto reciente [7] se comparó una pauta agresiva frente a una pauta menos agresiva. Los pacientes con la pauta agresiva tuvieron una mejoría clínica más rápida, pero se ha criticado que este estudio usaba una variable de resultado principal (mejoría clínica) que era muy dependiente de parámetros relacionados con hemodilución, por lo que en realidad se detectaba mayor hemodilución en pacientes que recibían más fluidos [8]. Por otra parte, varios estudios observacionales

de nuestro grupo [9, 10] y dos ensayos clínicos abiertos [11, 12] sugieren que la fluidoterapia agresiva tiene un efecto nulo o incluso perjudicial, pero estos ensayos clínicos tenían deficiencias relevantes en su diseño. Además, una pauta basada en metas (en inglés, *early goal-directed therapy*) no ha mostrado beneficios en el único ensayo publicado, dado que el estudio reclutó un número de pacientes insuficiente para cumplir con el tamaño muestral calculado [13]. Por todo ello, proponemos un ensayo clínico aleatorizado abierto y multicéntrico en pacientes con PA con el objetivo de evaluar una pauta de fluidoterapia agresiva precoz, frente a una pauta basada en las necesidades del paciente y más restrictiva, en variables clínicamente relevantes como la incidencia de PA moderada a grave. Dicho ensayo cuenta con la financiación necesaria ya que obtuvo una beca en concurrencia competitiva de la Acción Estratégica en Salud 2019 del *Instituto de Salud Carlos III* (PI19/01628), y la Beca *Gonzalo Miño* 2019 de la *Asociación Española de Gastroenterología*. Actualmente el ensayo se encuentra en las fases iniciales de reclutamiento (6 pacientes en junio de 2020) y el doctorando va a comenzar la inclusión de pacientes en el *Hospital Clínico Universitario Lozano Blesa.*

La cuarta y última línea de investigación será el estudio prospectivo de la influencia de los diferentes consumos de grasa en la dieta en la evolución de la PA, siendo una continuación del tercer capítulo de esta tesis "*Capítulo 3: Patrones de consumo de grasa en la dieta y curso clínico de la pancreatitis aguda en España"*, intentando mejorar algunas de sus limitaciones para confirmar de manera más firme sus resultados. En este sentido en vez de utilizar datos nutricionales regionales indirectos se obtendrán datos nutricionales prospectivos de manera directa de los propios pacientes ingresados con PA mediante un cuestionario dietético. Además, se evaluarán otros tipos de ácidos grasos como los PUFAs incluyendo la ratio omega-6/omega-3 y el índice de lipogénesis *de novo*. El estudio está en fase de diseño.

Por lo tanto, hay todavía un largo camino que andar y muchas preguntas que siguen sin respuesta en la PA. Tanto el doctorando como sus directores de tesis pretender continuar con su línea de trabajo e intentar responder, si es posible, a todas las preguntas formuladas y más que se irán planteando en el futuro conforme vayamos ahondando todavía más en el conocimiento sobre esta enfermedad.

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“La calidad nunca es un accidente; siempre es el

resultado del esfuerzo de la inteligencia”

John Ruskin