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GERÊNCIA DE ENSINO E PESQUISA
PROGRAMA DE PÓS-GRADUAÇÃO EM AVALIAÇÃO DE TECNOLOGIAS PARA O SUS
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WILLIAN PEGORARO KUS

ANÁLISE DE INCIDÊNCIA DE ISQUEMIA CEREBRAL TARDIA APÓS TRATAMENTO DE HEMORRAGIA SUBARACNÓIDE ANEURISMÁTICA EM ADULTOS JOVENS: ESTUDO DE COORTE

PORTO ALEGRE
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Dissertação apresentada como requisito parcial para obtenção do título de Mestre em Avaliação e Produção de Tecnologias para o SUS no Programa de Pós-graduação em Avaliação de Tecnologias para o SUS do Grupo Hospitalar Conceição.

Orientador: Prof. Dr. Paulo Valdeci Worm
Co-orientadora: Profª. Dra. Luciane Kopittke

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ATA DE APROVAÇÃO
(versão final - após defesa)

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"A verdadeira viagem de descobrimento
não consiste em procurar novas
paisagens, mas em ter novos olhos."
- Marcel Proust

RESUMO

Objetivo: Analisar a incidência de isquemia cerebral tardia e desfecho estratificado por idade em pacientes que sofreram hemorragia subaracnóide aneurismática. **Métodos:** Estudo de coorte com pacientes oriundos do Hospital Cristo Redentor/GHC no período de 2014 a 2020, com 359 pacientes eleitos separados em 2 grupos, 48 deles abaixo dos 40 anos e 311 com 40 anos ou mais. **Resultados:** Nos pacientes com idade abaixo de 40 anos, encontramos ICT em 81,3%, enquanto em pacientes com 40 anos ou mais foi 61,4%. Risco relativo de 1,32 (IC: 1,12 a 1,55), com p = 0,013. Após avaliação multivariada, na idade abaixo de 40 anos encontramos 27 a 39% mais risco de apresentar ICT. **Conclusão:** Identificamos a idade abaixo de 40 anos como fator de risco para ocorrência de ICT.

Palavras-chave: Aneurisma intracerebral; Hemorragia subaracnóide; Vasoespasmo intracraniano; Isquemia cerebral.

ABSTRACT

Objective: To analyze the incidence of delayed cerebral ischemia (DCI) and outcome stratified by age in patients who suffered aneurysmal subarachnoid hemorrhage. **Methods:** Cohort study with patients from Hospital Cristo Redentor/GHC from 2014 to 2020, with 359 patients chosen separated into 2 groups, 48 of them under 40 years of age and 311 aged 40 years or over. **Results**: In patients under 40 years of age we found DCI in 81.3%, while in patients aged 40 or over it was 61.4%. Relative risk of 1.32 (CI: 1.12 to 1.55), with p = 0.013. After multivariate assessment, in those under 40 years of age we found a 27 to 39% higher risk of presenting DCI. **Conclusion:** We identified age under 40 years as a risk factor for the occurrence of DCI.

Keywords: Intracerebral aneurysm; Subarachnoid hemorrhage; Intracranial vasospasm; Cerebral ischemia.

LISTA DE SIGLAS

ACA - Artéria Cerebral Anterior

ACI - Artérias Carótidas Internas

ACM - Artérias Cerebral Média

ACP - Artéria Cerebral Posterior

ACoA - Artéria Comunicante Anterior

ACoP - Artéria Comunicante Posterior

AB - Artéria Nasilar

AngioTC - Angiotomografia dos Vasos Cerebrais

AV - Artérias Vertebrais

AVC - Acidente Vascular Cerebral

cGMP - Monofosfato de Guanosina

F - Escala de Fisher

FM - Escala de Fisher modificada

GC - Guanilato Ciclase

GHC – Grupo Hospitalar Conceição

GOS - Glasgow Outcome Scale

HIC - Hemorragia Intracerebral

HH - Escala de Hunt-Hess

HSA - Hemorragia Subaracnóide

HSAa - Hemorragia Subaracnóide Aneurismática

HSAt - Hemorragia Subaracnóide Traumática

ICT - Isquemia Cerebral Tardia

LCR - Líquido Cefalorraquidiano

ON - óxido nítrico

SNC - Sistema Nervoso Central

SPSS - Statistical Package for the Social Science

SUS - Sistema Único de Saúde

WFNS - Escala da World Federation of Neurological Surgeons

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APRESENTAÇÃO

Este trabalho está inserido na linha de pesquisa Avaliação e Produção de Tecnologias na Atenção em Saúde do Programa de Pós-graduação em Avaliação de Tecnologias para o Sistema Único de Saúde (SUS), sendo a dissertação apresentada como requisito parcial para a obtenção do título de Mestre em Avaliação e Produção de Tecnologias para o SUS.

A linha de pesquisa envolve estudos sobre a produção e avaliação de tecnologias que se destinam aos processos de saúde-doença-cuidado, assim como pesquisas relacionadas ao custeio, à eficácia, à efetividade e à segurança dos modelos tecno assistenciais em saúde (GEP, 2021).

O Mestrado Profissional em Avaliação e Produção de Tecnologias para o SUS propõe-se a contribuir com a formação de profissionais que atuam nas áreas de gestão, assistência e educação, desenvolvendo habilidades e capacidades tecno científicas compatíveis para o fortalecimento do SUS (GEP, 2021). As tecnologias em saúde englobam medicamentos, materiais, equipamentos e procedimentos; sistemas organizacionais, educacionais, de informação e de suporte; e programas e protocolos assistenciais, por meio dos quais a atenção e os cuidados com a saúde são prestados à população (GOODMAN, 2014).

A realização desta pesquisa permitiu a elaboração de sugestões para modificações pertinentes aos pacientes com hemorragia subaracnóide aneurismática (HSAa) no protocolo de assistência em vigor no Grupo Hospitalar Conceição (GHC). Permitiu também a elaboração de artigo científico para publicação *a posteriori* e a construção de um banco de dados robusto para facilitar pesquisas futuras neste que é o serviço de referência para o tratamento de aneurismas cerebrais no estado do Rio Grande do Sul.

1 INTRODUÇÃO

A hemorragia subaracnóide (HSA) não traumática é uma forma grave de acidente vascular cerebral, caracterizada por sangramento arterial abrupto no espaço subaracnóide. A causa em 80% dos casos é a ruptura de um aneurisma cerebral. A taxa de letalidade geral da HSAa é de 32 a 67% (HUANG, GELDER, 2002). Além disso, aproximadamente 30% dos sobreviventes apresentarão incapacidade moderada ou grave (HOP et al., 1997).

A incidência de HSA é controversa e variável na literatura mundial. O Japão apresenta incidência de 22,7 casos por 100 mil habitantes por ano, a Finlândia registra 19,7. Na América do Sul e Central, 4,2 casos por 100 mil habitantes por ano. Tais discrepâncias não se devem apenas às diferenças étnicas, mas também ao grau variável de eficiência dos sistemas de saúde e vigilância que pode implicar em erro diagnóstico e subnotificação. Estima-se que mulheres apresentam uma chance 1,24 vezes maior do que homens. Esta diferença ocorre apenas a partir da sexta década. De maneira geral, os fatores etiológicos da HSAa em pacientes de meia-idade e idosos, como hipertensão arterial, não são comuns aos pacientes com menos de 40 anos (OGUNGBO, 2003; LAWTON, VATES, 2017).

Além disso, se sabe que a taxa de ruptura aneurismática aumenta com a idade (JEE et al., 2020), tendo o pico de incidência entre a quinta e a sexta década de vida (KRINGS, GEIBPRASERT, TERBRUGGE, 2010). Sendo assim, a ocorrência de HSAa em pacientes com menos de 40 anos é incomum. Entretanto, é a forma de acidente vascular cerebral de maior impacto em adultos jovens (ROOIJ et al., 2007). As consequências neurológicas podem variar desde declínio cognitivo leve até quadros de incapacidade severa. Neste grupo etário a patologia apresenta importantes implicações socioeconômicas por reduzir anos potencialmente produtivos de uma população com uma alta expectativa de vida (OGUNGBO, 2003).

De maneira geral, os fatores etiológicos e prognósticos da HSAa em pacientes de meia-idade e idosos não são comuns aos pacientes com menos de 40 anos (KRINGS, GEIBPRASERT, TERBRUGGE, 2010; JEE et al., 2020).

Oppong et al. (2018) encontrou a variável idade mais jovem como preditor independentemente para ocorrência de vasoespasmo, OR = 1,03 por ano de redução com intervalo de confiança 95%, 1,01–1,05, e $p < 0,001$. Pacientes de idade

menor de 55 anos apresentaram risco significativamente maior de vasoespasmo em relação aos mais velhos.

As pesquisas direcionadas a esta população são limitadas e escassas. Por isso, é fundamental dirigir nosso estudo para potencializarmos medidas políticas de saúde pública que aumentem a qualidade no atendimento desta população. As pesquisas direcionadas a essa população são limitadas e escassas. Por isso, é fundamental dirigir nosso estudo para potencializarmos medidas políticas de saúde pública que aumentem a qualidade no atendimento desta população.

2 OBJETIVOS

2.1 OBJETIVO GERAL

Analisar a incidência de isquemia cerebral tardia da HSA aneurismática em pacientes adultos até 40 anos tratados por microcirurgia ou cirurgia endovascular, comparando-os com pacientes de faixas de idade mais elevadas.

2.2 OBJETIVOS ESPECÍFICOS

- Avaliar o desfecho radiológico realizado baseada no índice de isquemia cerebral tardia (ICT) decorrida do vasoespasmo após a ruptura aneurismática.

- Analisar o índice de retorno ao trabalho nos pacientes egressos com finalidade de ampliar o conhecimento sobre esta doença, possibilitando o desenvolvimento de políticas públicas de inclusão desta população.

3 REFERENCIAL TEÓRICO

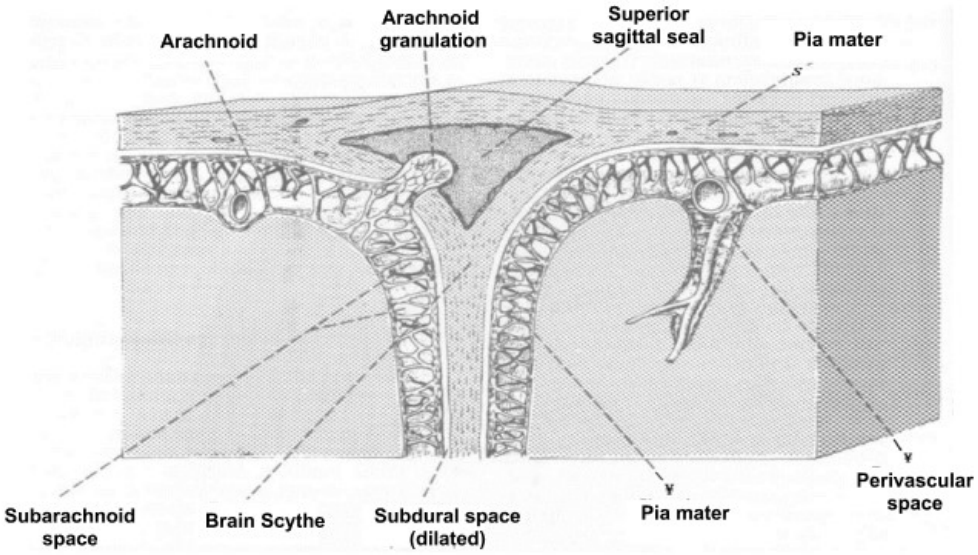
3.1. ANATOMIA DO SISTEMA NERVOSO CENTRAL

O sistema nervoso central (SNC) é em sua totalidade recoberto por membranas denominadas meninges. Para avaliar suas características as separamos em três: dura-máter, aracnóide e pia-máter (DRIETRICH, DACEY, 2000).

Externamente encontra-se a dura-máter, mais espessa, rica em fibras colágenas e bem vascularizada. No encéfalo, a principal artéria que irriga a dura-máter é a artéria meníngea média, ramo da artéria maxilar. Também é ricamente inervada, diferente das outras camadas meníngeas. Basicamente a sensibilidade intracraniana se localiza na dura-máter, pois o parênquima encéfalo não possui terminações nervosas sensitivas, sendo ela a responsável pelas dores de cabeça (MACHADO, 2007).

A aracnóide é uma membrana delicada que se localiza interposta entre a dura-máter e a pia-máter, constituindo o espaço subaracnóideo (Figura 1), responsável por abrigar o líquido cefalorraquidiano (LCR). Além disso, existem no espaço subaracnóideo delicadas trabéculas denominadas trabéculas aracnóideas. Estas recebem o nome pois seu aspecto lembra a teia de uma aranha (MACHADO, 2007).

Figura 1. Secção transversal do seio sagital superior mostrando a granulação aracnóideia, a disposição das meninges e dos espaços meníngeos.



Fonte: Adaptado de Machado, 2007.

Este espaço se compartimenta em áreas de dilatação formando áreas com maior quantidade liquórica denominadas cisternas subaracnóideas, as quais fornecem o sítio cirúrgico principal nas intervenções neurocirúrgicas para abordagem de aneurismas. As áreas cisternais do espaço subaracnóideo constituem-se por uma separação mais pronunciada entre as meninges aracnóide-máter e pia-máter, contém trabéculas aracnóideas com LCR, nervos cranianos e a intensa rede vascular do encéfalo (MACHADO, 2007).

As cisternas são fundamentais na circulação do LCR pelo cérebro. Primeiramente o LCR é produzido dentro dos ventrículos laterais nos plexos coróides, então desce através dos forames de Monro até o terceiro ventrículo, atravessa o aqueduto cerebral e ganha o quarto ventrículo, de onde, através de aberturas chamadas forames de Luschka, lateralmente, e de Magendie, medialmente, ganha o espaço subaracnóide banhando o tronco cerebral, cerebelo, cérebro e demais estruturas encefálicas além da medula espinhal e raízes da cauda equina na coluna lombossacra. As principais cisternas subaracnóideas são as seguintes: Cisterna Ambiente; Cisterna Calosa; Cisterna Carótida; Cisterna Quiasmática; Cisterna Crural; Cisterna Interpeduncular; Cisterna Cerebelomedular Lateral; Cisterna da Lâmina Terminal; Cisterna Magna; Cisterna Olfatória; Cisterna Prepontina; Cisterna Quadrigeminal; Cisterna Silviana (LAWTON, 2011).

Por vezes a separação destas cisternas é a critério puramente anatômico, tendo em vista os espaços estarem distribuídos de forma contínua e nem sempre haver uma estrutura os separando. Normalmente elas são nomeadas a partir de estruturas relacionadas. A intercomunicação entre as cisternas também drena o LCR

até a sua reabsorção pelas granulações aracnóideas, principalmente no seio sagital superior, tendo como principal via de saída a veia jugular interna, mas também a rede linfática cervicofacial. Envolvendo as estruturas arteriais, além do espaço subaracnóideo, invaginações do espaço subpial formam uma bainha de revestimento sobre as artérias, estrutura chamada de espaço de Virchow-Robin. O método de dissecção subaracnóide abre e interliga essas cisternas a caminho de um aneurisma, por exemplo (LAWTON, 2011).

O conhecimento da vascularização cerebral é essencial para que se possa compreender os danos oriundos dos eventos vasculares. A vascularização cerebral é oriunda inicialmente do arco aórtico, em que à nível da articulação esternoclavicular o primeiro e maior dos seus ramos, a artéria braquiocefálica direita, bifurca-se em 2 ramos terminais: artéria subclávia direita e artéria carótida comum direita, enquanto a artéria carótida comum esquerda se origina diretamente do ápice do arco aórtico, imediatamente distal à origem da artéria braquiocefálica. Bilateralmente, ambas artérias carótidas comuns se bifurcam, aproximadamente à nível de C5, em artérias carótidas externas, responsável pela vascularização de boa parte das estruturas da cabeça excluindo-se cérebro e elementos orbitários, e artérias carótidas internas (ACI). Estas, por sua vez, são primariamente divididas segundo Bouthillier em sete segmentos, sendo eles: cervical, petroso, lacerum, cavernoso, clinóide, oftálmico e comunicante. Logo abaixo da substância perfurada anterior, a ACI se bifurca em artérias cerebral média (ACM), maior, e artéria cerebral anterior (ACA), com metade do diâmetro (OSBORN, 1999).

A ACA é dividida em 5 segmentos, sendo A1 e A2 os segmentos proximais, enquanto, a partir de A3, os segmentos distais. Existe ainda uma artéria denominada de comunicante anterior (ACoA) que realiza a ligação entre cada uma das artérias cerebrais anteriores, comunicando na altura da A1-A2 ambos os lados do sistema arterial carotídeo. A ACM possui 4 segmentos: horizontal (M1), insular (M2), opercular (M3) e ramos corticais (M4) (OSBORN, 1999).

Ramos das artérias subclávias, as artérias vertebrais (AV), uma de cada lado, ascendem pela coluna vertebral através dos forames transversos até a fossa posterior, na base do crânio, onde se unem para formar a artéria basilar (AB). Ainda na fossa posterior, 3 artérias dividem o território a ser nutrido: a. cerebelar superior; PICA, ou a. cerebelar posteroinferior e AICA, a. cerebelar anteroinferior. A AB ascende e se bifurca em artérias cerebrais posteriores (ACP) direita e esquerda. A

ACP pode ser dividida em 5 segmentos: pré-comunicante (P1), pós-comunicante (P2), quadrigeminal (P3), cortical (P4) e ramos terminais (P5) (OSBORN, 1999).

A artéria comunicante posterior (ACoP) origina-se na porção posterior do segmento comunicante da ACI e anastomosa-se com a artéria cerebral posterior (ACP), assim conectando a circulação anterior à posterior. O conjunto que surge desta união é chamado de Polígono de Willis, a estrutura principal de vascularização cerebral (OSBORN, 1999).

3.2. EVENTOS VASCULARES

O acidente vascular cerebral (AVC) ocorre quando existe uma alteração do fluxo sanguíneo cerebral, aguda e espontânea, capaz de causar perda de parênquima cerebral e assim dano neurológico. Classificados conforme sua etiologia como isquêmico ou hemorrágico (PONTES-NETO et al., 2009).

O AVC isquêmico é responsável por 80 a 85% dos casos de AVC, causado por interrupção do fluxo de uma artéria cerebral por embolismo ou trombose. O AVC hemorrágico ocorre pelo extravasamento de sangue arterial para o exterior da estrutura vascular, gerando aumento da pressão intracraniana e déficit de fluxo sanguíneo mesmo em áreas não afetadas diretamente pelo hematoma (QURESHI et al., 2001).

São três os tipos de AVC hemorrágico:

- Hemorragia intracerebral (HIC), também chamada de hematoma intraparenquimatoso, pode ter origem da lesão nas pequenas artérias penetrantes causada por hipertensão arterial sistêmica ou angiopatia amilóide. Ou ainda pode ser secundária a uma lesão preexistente, como as malformações arteriovenosas.
- Hemorragia intraventricular, que de forma isolada é um importante causa de sangramento na fase neonatal, sobretudo em prematuros. Pode também ocorrer concomitante a hemorragia subaracnóidea ou a um HIC periventricular com acometimento ependimário e extravasamento para o interior do sistema ventricular.
- Hemorragia subaracnóide (HSA), representando apenas 5% dos AVC, porém sua mortalidade na fase aguda e subaguda pode chegar a 50% (SIQUEIRA, SOUZA, VELLUTINI, 2016).
- Por definição, AVC hemorrágico tem origem não traumática. As hemorragias traumáticas, como hematomas epidurais, hematomas subdurais, hemorragia subaracnóide traumática (HSAt), mesmo com potencial de gerar dano neurológico não são classificadas como AVC, pois tipicamente estão associadas com trauma agudo ou subagudo. Se nos referirmos à totalidade das HSA, a traumática é majoritária em frequência. Porém, ao se referir genericamente ao evento HSA, assim como para outros AVC hemorrágicos, se trata de uma HSA não traumática (SIQUEIRA, SOUZA, VELLUTINI, 2016).

Na HSA, em 80% dos casos a ruptura de aneurismas é a causa do sangramento, chamamos então de HSAa. A incidência de HSA é controversa e

variável na literatura mundial. O Japão apresenta incidência de 22,7 casos por 100 mil habitantes por ano, a Finlândia registra 19,7. Na América do Sul e Central, 4,2 casos por 100 mil habitantes por ano. Tais discrepâncias não se devem apenas as variabilidades étnicas, mas também ao grau variável de eficiência dos sistemas de saúde e vigilância que pode implicar em erro diagnóstico e na subnotificação. Estima-se que mulheres apresentam uma chance 1,24 vezes maior do que homens. Esta diferença ocorre apenas a partir da sexta década. De maneira geral, os fatores etiológicos da HSAa em pacientes de meia-idade e idosos, como hipertensão arterial, não são comuns aos pacientes com menos de 40 anos (OGUNGBO, 2003; LAWTON, VATES, 2017).

Sabe-se que a taxa de ruptura aneurismática aumenta com a idade, tendo o pico de incidência entre a quinta e a sexta década de vida (KRINGS, GEIBPRASERT, TERBRUGGE, 2010; JEE et al., 2020). Sendo assim, a ocorrência de HSAa em pacientes com menos de 40 anos é incomum. Entretanto, é a forma de acidente vascular cerebral de maior impacto em adultos jovens. (ROOIJ et al., 2007) As consequências neurológicas podem variar desde declínio cognitivo leve até quadros de incapacidade severa. Neste grupo etário a patologia apresenta importantes implicações socioeconômicas por reduzir anos potencialmente produtivos de uma população com uma alta expectativa de vida (OGUNGBO, 2003).

3.3. O ANEURISMA CEREBRAL

O sistema vascular cerebral é constituído por estruturas vasculares distintas. Enquanto a artéria leva sangue rico em oxigênio e glicose ao tecido encefálico e demais estruturas que o envolvem, as veias e seios venosos são responsáveis por encaminhar o sangue venoso, pobre em oxigênio, mas rico em gás carbônico e metabólitos, de volta ao coração.

A artéria intracraniana saudável é constituída por 3 camadas, íntima, média e adventícia. Internamente, a íntima forma o lúmen arterial por uma camada simples de células endoteliais seguida então por uma membrana de fibras elásticas, chamada de lâmina elástica interna. A camada média possui fibras musculares lisas e colágeno tipo III. Externamente, a adventícia é constituída por colágeno tipo I, elastina, fibroblastos e pequenos vasos de nutrição para esta espessa parede chamados de *vasa vasorum*. As artérias extracranianas ainda possuem uma

camada elástica externa situada entre a camada média e adventícia (SIQUEIRA, SOUZA, VELLUTINI, 2016).

A formação do aneurisma cerebral está associada a estresse hemodinâmico, quando elevadas forças de cisalhamento atuam sobre a parede arterial evoluindo com ruptura da lâmina elástica interna, enfraquecendo estruturalmente esta parede. Em resposta ao estresse sofrido ocorre um processo adaptativo denominado de hiperplasia miointimal, com espessamento da parede, alterações evidenciadas em aneurismas não rotos (SIQUEIRA, SOUZA, VELLUTINI, 2016).

Quando não ocorre ruptura do aneurisma nesta fase inicial, onde há o crescimento da lesão, em certo momento haverá redução da força de cisalhamento exercida na parede, com hipofluxo e aumento do tempo de contato entre o sangue e o endotélio lesado, então desenvolvendo reação inflamatória responsável por remodelamento e maior crescimento do aneurisma. Nesta fase pode ocorrer também formação de placas ateroscleróticas (SIQUEIRA, SOUZA, VELLUTINI, 2016).

O enfraquecimento da parede é potencializado por ação de infiltrado inflamatório e proteases degradadoras de matriz extracelular, uma rede complexa de proteínas e proteoglicanos sintetizadas pelas células locais e responsável pelo suporte estrutural arterial. Entre as principais proteases estão a metaloproteinases 2 e 9, degradam elastina e colágeno. Células apoptóticas são infrequentes na parede arterial saudável, mas muito encontradas em aneurismas rotos, em maior quantidade próximas ao local da ruptura, além de macrófagos, células T e B, imunoglobulinas e complemento ativado (SIQUEIRA, SOUZA, VELLUTINI, 2016).

Quanto à localização dos aneurismas, dados do ISUIA (1998), com 4.600 indivíduos portadores de aneurismas não rotos, a artéria carótida interna foi a localização mais frequente (29,9%), excluindo segmento cavernoso e ACoP. A ACM apresentou 29,1% das lesões, a ACoA 12,3% e a ACoP apenas 8,5%.

Por outro lado, Forget et al. (2001) constatou a posição de maior frequência de ruptura na ACoA, com 29%. Em segundo lugar a ACoP, com 19%, seguido da ACM, com 11%. Este padrão também foi evidenciado por outros estudos, como o ISAT (MOLYNEUX et al., 2002).

3.4. COMPLICAÇÕES DA HSAA

Duas situações especiais contribuem para a morbimortalidade relacionadas à HSA, a lesão cerebral precoce e o vasoespasmo cerebral (CIUREA et al., 2013). É considerada lesão cerebral precoce aquela ocorrida dentro de 72 horas da ruptura aneurismática e causada por aumento agudo da pressão intracraniana com diminuição do fluxo sanguíneo cerebral, com consequente edema cerebral e inflamação.

A HSA também pode ocasionar vasoespasmo cerebral, um estreitamento transitório e autolimitado de vasos arteriais. Este fenômeno está associado à isquemia cerebral tardia (ICT) (CIUREA et al., 2013). Nesses casos, além da quantidade em volume do sangramento, a localização do aneurisma pode alterar a intensidade dos eventos posteriores. Quanto mais proximal forem as artérias atingidas pelo sangue extra luminal maior seu calibre, então mais vasos distais poderão ser afetados pela hipoperfusão. Consequentemente, mais regiões estarão sob risco de isquemia e, assim, maiores as chances de sequelas neurológicas.

O período para seu surgimento costuma iniciar em 3 dias após a HSA, com pico de incidência nos dias 6 e 8 e pode se prolongar de 2 a 3 semanas. Há forte associação com declínio clínico causado por isquemia cerebral tardia em 20 a 30% dos casos (SIQUEIRA, SOUZA, VELLUTINI, 2016).

3.5. FISIOPATOLOGIA DO VASOESPASMO

O fluxo sanguíneo cerebral é afetado pela HSA através do vasoespasmo, aumentando a resistência cerebrovascular e afetando a autorregulação, aumentando a suscetibilidade com reduções transitórias na pressão de perfusão cerebral com risco de hipofluxo e isquemia (DIETRICH, DACEY, 2000).

A regulação do tônus das células de músculo liso vascular pelos filamentos de actina e miosina é feita pelo reservatório de cálcio intracelular. O cálcio pode ter duas fontes principais, o influxo do meio extracelular, regulado por canais de cálcio na membrana, ou ainda o cálcio pode ser liberado pelo retículo sarcoplasmático através de aumento do inositol 1,4,5-trifosfato ou da ativação de receptores sensíveis à rianodina (DIETRICH, DACEY, 2000).

O monofosfato de guanosina cíclico (cGMP) atua na membrana sarcoplasmática ativando bombas de cálcio e removendo cálcio, causando relaxamento de células musculares lisas. O óxido nítrico (ON) é o principal ativador do cGMP produtor de guanilato ciclase (GC) (DIETRICH, DACEY, 2000).

A HSA afeta o fluxo sanguíneo cerebral principalmente por mecanismos endoteliais. Evidencia-se prejuízo no relaxamento endotélio-dependente, aumento da produção de fatores constritores derivados do endotélio e ainda atividade prejudicada dos canais de potássio (DIETRICH, DACEY, 2000).

Os principais componentes sanguíneos responsáveis por comprometer o endotélio são a oxiemoglobina e a bilirrubina, com a oxiemoglobina ainda eliminando o ON, inativando o GC e aumentando a produção de radicais livres de oxigênio (DIETRICH, DACEY, 2000).

Após eliminado de células endoteliais, o ON se difunde para células musculares lisas e ativa o GC, que produz cGMP. Este é responsável por ativar bombas intracelulares de cálcio, sequestrando cálcio livre nas reservas intracelulares causando relaxamento de músculo liso. A eliminação do ON resulta numa redução da atividade do GC, causando vasoespasmo (DIETRICH, DACEY, 2000).

Ainda no contexto de HSA, compostos ferrosos como a hemoglobina produzem radicais livres de oxigênio e causam vasoespasmo danificando células endoteliais e musculares lisas, aumentando a permeabilidade endotelial e alterando os níveis intracelulares de cálcio e inositol 1,4,5-trifosfato (DIETRICH, DACEY, 2000).

Também foi observado células musculares lisas despolarizadas após HSA, devido a esgotamento energético ou por inibição dos canais de potássio, gerando despolarização da membrana e então a vasoconstrição (DIETRICH, DACEY, 2000).

Nesse contexto, o vasoespasmo e a ICT são dois importantes mecanismos para estabelecimento de lesão cerebral após hemorragia subaracnóide aneurismática.

3.6. ESCALAS DE CLASSIFICAÇÃO

Os pacientes com HSAa são avaliados utilizando-se escalas previamente estabelecidas, capazes de definir a gravidade de apresentação e riscos de

complicações. São elas:

3.6.1 Escala de Hunt-Hess (HH)

A escala de Hunt-Hess (WARE, KOSINSKI, KELLER, 1996), é a ferramenta clássica utilizada para estratificar o paciente com HSA do ponto de vista neurológico com comprovado valor preditor de sobrevida. Doenças sistêmicas graves, como hipertensão, diabetes, arteriosclerose grave, doença pulmonar crônica e vasoespasmo grave na arteriografia resultam na colocação do paciente na próxima categoria menos favorável.

- Grau 1: Assintomático ou dor de cabeça mínima e rigidez nucal leve;
- Grau 2: Dor de cabeça moderada a grave e rigidez nucal. Paralisia de NC sem outro déficit neurológico;
- Grau 3: Sonolência, confusão mental ou déficit neurológico focal leve;
- Grau 4: Estupor, hemiparesia moderada a grave, rigidez precoce em descerebração, distúrbios vegetativos;
- Grau 5: Coma profundo, rigidez em descerebração, aparência moribunda.

3.6.2 Escala da WFNS

A Federação Mundial de Neurocirurgia (*World Federation Neurosurgery* - WFNS), em 1988, propôs o desenvolvimento de uma nova escala para classificar os pacientes com HSA utilizando o escore de Glasgow para avaliação de nível de consciência e a presença ou ausência de déficit neurológico focal (TEASDALE et al., 1988). Abaixo as classificações:

- Grau 1: Escala de coma de Glasgow 15 sem hemiparesia;
- Grau 2: Escala de coma de Glasgow 13-14 sem hemiparesia;
- Grau 3: Escala de coma de Glasgow 13-14 com hemiparesia;
- Grau 4: Escala de coma de Glasgow 7-12 com ou sem hemiparesia;
- Grau 5: Escala de coma de Glasgow 3-6 com ou sem hemiparesia.

3.6.3 Escala de Fisher (F)

A Escala de Fisher (FISHER, KISTLER, DAVIS, 1980) é utilizada para

estratificar o sangramento visualizado na tomografia computadorizada (TC) de crânio e relacionar com o risco de vasoespasmo. Dividindo os pacientes em 4 grupos, de I a IV, sendo o tipo III aquele que apresenta maior associação com vasoespasmo clínico e angiográfico:

- Grau 1: Nenhum sangue subaracnóide detectado;
- Grau 2: Sangramento difuso ou sangue no espaço subaracnóide com < 1 mm de espessura;
- Grau 3: Coágulo localizado ou sangue no espaço subaracnóide com > 1mm de espessura;
- Grau 4: Coágulo intraventricular ou intraparenquimatoso com ou sem HSA difusa.

3.6.4 Escala de Fisher modificada (Fm)

Após o estudo de Claassen (CLAASEN et al., 2001), com um modelo relacionando vasoespasmo sintomático com múltiplas variáveis independentes na HSAa, se propôs a modificação da escala de Fisher, onde o risco de vasoespasmo é crescente:

- Grau 1: Hemorragia fina (< 1 mm), focal ou difusa, sem hemorragia intraventricular, chance de vasoespasmo de 24%;
- Grau 2: Hemorragia fina (< 1 mm), focal ou difusa, com hemorragia intraventricular, chance de vasoespasmo de 33%;
- Grau 3: Hemorragia espessa (> 1 mm), focal ou difusa, sem hemorragia intraventricular, chance de vasoespasmo de 33%; e
- Grau 4: Hemorragia espessa (> 1 mm), focal ou difusa, com hemorragia intraventricular, chance de vasoespasmo de 40%.

3.6.5 Escala GOS

A escala GOS (*Glasgow Outcome Scale*) (JENNETT, BOND, 1975) é amplamente utilizada para avaliar o resultado a longo prazo de pacientes graves com lesão cerebral, levando em conta sequelas físicas, cognitivas e sociais.

1 - Morte;

2 - Estado vegetativo;

3 - Incapacidade severa - capaz de seguir comandos, incapaz de viver independentemente;
4 - Incapacidade moderada - capaz de viver independentemente, incapaz de voltar ao trabalho ou escola; e
5 - Incapacidade leve / boa recuperação - capaz de voltar ao trabalho ou escola.

Após o acompanhamento clínico, a classificação se dá em três categorias:

a) Recuperado, déficit neurológico mínimo, GOS 5;
b) Parcialmente recuperado, vida diária independente, GOS 4; e
c) Não recuperado, dependência severa, coma e morte, GOS 1-3.

4 PRODUTOS TÉCNICOS

Primeiramente, através desta pesquisa um robusto banco de dados foi criado e ficará disponível para que demais pesquisadores possam avaliar outros pontos de interesse relacionados a pacientes operados no HCR após HSAa, devido ao período de seleção de 7 anos.

Além deste, dois artigos científicos enviados às revistas *Journal of Stroke & Cerebrovascular Diseases* e *World Neurosurgery* aguardam resposta quanto à publicação.

PRODUTO 1 – ARTIGO DE REVISÃO

Journal of Stroke and Cerebrovascular Diseases

Aneurysmal Subarachnoid Hemorrhage in Young Adults: A literature Review

--Manuscript Draft--

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Abstract:	Objective: Analyze the difference in the rate of late cerebral ischemia after aneurysmal subarachnoid hemorrhage, comparing groups of patients according to the age. Methods: A literature review was carried out in the main databases in the last 10 years. Results: Only articles with analysis by age were selected. Of the 169 articles found, 3 were included in the analysis. We found a higher risk of young adults having vasospasm and cerebral ischemia after aneurysmal subarachnoid hemorrhage. Conclusion: Advancing age is a protective factor for the occurrence of cerebral ischemia after aneurysmal subarachnoid hemorrhage.
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Aneurysmal Subarachnoid Hemorrhage in Young Adults: A literature Review

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Abstract

Objective: Analyze the difference in the rate of late cerebral ischemia after aneurysmal subarachnoid hemorrhage, comparing groups of patients according to the age. **Methods:** A literature review was carried out in the main databases in the last 10 years. **Results:** Only articles with analysis by age were selected. Of the 169 articles found, 3 were included in the analysis. We found a higher risk of young adults having vasospasm and cerebral ischemia after aneurysmal subarachnoid hemorrhage. **Conclusion:** Advancing age is a protective factor for the occurrence of cerebral ischemia after aneurysmal subarachnoid hemorrhage.

Introduction:

Non-traumatic subarachnoid hemorrhage (SAH) is a cerebrovascular disease characterized by sudden arterial bleeding into the subarachnoid space. approximately 80% of cases are caused by a brain aneurysm. The overall mortality rate of aneurysmal SAH (aSAH) ranges from 32 to 67%.(1) In addition, approximately 30% of survivors will have moderate or severe neurological disability.(2)

The incidence of SAH is controversial and variable in the literature. Japan has an incidence of 22.7 cases per 100,000 inhabitants per year, Finland registers 19.7. In South and Central America, 4.2 cases per 100,000 inhabitants per year. Such discrepancies are not only due to ethnic variability, but also different structures of health systems that may result in diagnostic error and underreporting. It is estimated that women are 1.24 times more likely than men to develop brain aneurysms, but this difference occurs only after the sixth decade of life. In general, the most common etiological factors for aSHA in middle-aged patients are not present in the young population, such as arterial hypertension (3)(4)

Aneurysmal rupture increases with age,(5) and the peak incidence occurs between the 5th and sixth decade of life.(6) The occurrence of aSAH in patients younger than 40 years is very uncommon, and causes a great functional impact on the lives of these patients dure to neurological disability.(7) The neurological consequences range from mild cognitive decline to severe motor disability. In this age group, aSHA has important socioeconomic

implications as it reduces potentially productive years in a population with a high life expectancy.(3)

The clinical presentation aSAH is characterized by severe headache with sudden onset, but it occurs in only 36% of cases. Meningeal irritation, nausea, vomiting, focal neurological deficits and decreased level of consciousness may be associated. In addition, the condition may be preceded, in one week to two months, by sentinel headache, of lesser intensity and usually improves within 24 hours. This clinical sign is an important semiological predictor of aneurysmal rupture.(8)

Immediate recognition of such a condition is very important for the investigation, since the brain CT is normal in 9% of patients with aSAH, and its recognition will depend on a lumbar puncture.(9) Up to 70% of patients with aSAH will present vasospasm, a vascular phenomenon of arterial narrowing visualized by angiography, which occurs predominantly between 7 and 10 days after bleeding ictus. Furthermore, it constitutes the main cause of disability and death in patients with ruptured aneurysms.(7)

The available medical literature on aSAH, in general, is based on populations not stratified by age groups. Considering the increase in the incidence of aSAH with age, the understanding of the pathology is mainly based on data concerning the elderly population. The current literature lacks data on younger age groups, where neurological sequelae have the greatest impact in terms of loss of potentially productive years and where the occurrence of late cerebral ischemia is higher.(10) Therefore, the main objective of this review of literature was to analyze the difference in the risk of late cerebral ischemia, the main aggregating factor of neurological sequelae, after Aneurysmal SAH by age, considering the fact that young patients present characteristics of clinical evolution.(10)

Material and Methods

We carried out a bibliographic review to analyze delayed cerebral ischemia after aSAH from the perspective of patients' age. Through the PICO strategy, we have:

P: Young adult patients after aneurysmal subarachnoid hemorrhage C: Elderly patients

O: Delayed cerebral ischemia

We carried out the research in Pubmed/Medline, Lilacs, Epistemonikos, *Biblioteca Virtual e Saúde* and Scielo using the following descriptors:

1. Subarachnoid hemorrhage
2. Cerebral ischemia
3. Intracerebral aneurysm
4. Age

Articles with more than 10 years of publication and those without analysis by patients age were excluded. There was no exclusion due to the article language. Patients with aSAH are evaluated using previously established scales that define the severity of presentation and risks of complications as follows:

Hunt-Hess scale

The Hunt-Hess scale (11) is used to stratify patients with aSAH from the neurological examination, with a predictive value for survival rate. Systemic diseases such as hypertension, diabetes, arteriosclerosis, chronic lung disease, result in placing the patient in a least favorable classification, as well as severe vasospasm on arteriography.

Grade I: Asymptomatic or minimal headache and mild nuchal stiffness;

Grade II: Moderate to severe headache and neck stiffness. Cranial nervde palsy without other neurological deficit;

Grade III: Drowsiness, mental confusion or mild focal neurological deficit; Grade IV: Stupor or moderate to severe motor deficit

Grade V: Deep coma or decerebration

World Federation of Neurological Surgeons - WFNS scale

The aSAH clinical classification scale proposed by the World Federation of Neurological Surgeons (WFNS)(12) evaluate the patient's level of consciousness upon admission and the occurrence of motor deficit.

Grade I: Glasgow 15 without motor deficit; Grade II: Glasgow 14-13 without motor deficit; Grade III: Glasgow 14-13 with motor deficit;

Grade IV: Glasgow 12-7 with or without motor deficit; Grade V: Glasgow 6-3 with or without motor deficit.

Fisher scale

The Fisher Scale(13) is used to stratify the amount of bleeding visualized on cranial computed tomography (CT) and relate it to the risk of vasospasm. Dividing the patients into 4 groups, from I to IV, with type III being the one with the greatest association with clinical and angiographic vasospasm.

Grade 1: No subarachnoid blood detected;

Grade 2: Diffuse bleeding or blood in the subarachnoid space with < 1 mm thickness; Grade 3: Localized clot or blood in the subarachnoid space with > 1 mm thickness Grade 4: Intraventricular or intraparenchymal blood with or without diffuse SAH.

Modified Fisher scale

After the study by Claasen(14), with a model relating symptomatic vasospasm with multiple independent variables in aSAH, a modification of Fisher's scale was proposed, where the risk of vasospasm is increasing in proportion to the degree:

Grade 1: Thin hemorrhage (< 1 mm), focal or diffuse, without intraventricular hemorrhage, 24% chance of vasospasm;

Grade 2: Thin hemorrhage (< 1 mm), focal or diffuse, with intraventricular hemorrhage, 33% chance of vasospasm;

Grade 3: Thick hemorrhage (> 1 mm), focal or diffuse, without intraventricular hemorrhage, 33% chance of vasospasm;

Grade 4: Thick (> 1 mm) hemorrhage, focal or diffuse, with intraventricular hemorrhage, 40% chance of vasospasm.

Results

A total of 167 articles were selected initially and, subsequently, another 2 were included based on citations in the references of the selected articles. Of these 169 articles, 3 were selected based on inclusion criteria

In Lai's cohort,(15) with 328 patients, the age criteria had a cut-off point of 55 years. In this subgroup, women under 55 years had a higher rate of angiographic vasospasm (b = 0.56; 95% confidence interval, 0.19 – 0.93; p = 0.003).

For Oppong,(16) in a cohort of 994 patients, younger age was an independent predictor for the occurrence of vasospasm, with an OR = 1.03 per year of reduction with 95% confidence interval (1.01–1.05, and p < 0.001). When separated into 2 groups, patients younger than 55 years old had a significantly higher risk of vasospasm compared to older patients. Women had an OR = 1.84 (95% confidence interval 1.28–2.67, and p = 0.001) while men had an OR = 2.63; (95% confidence interval; 1.38–5.01, and p = 0.003).

On the other hand, when these patients were separated into 3 groups (under 55 years old, 55 to 74 years old and over 74 years old), this study demonstrated an interesting relationship between vasospasm and the female sex. In men, patients in the younger group (<55 years) had a higher risk of vasospasm, which was reduced in the second group (55

- 74 years) and in the third (>74 years). In women, the risk remained high from the first to the second group, having reduced only in the age group > 74 years. This higher risk in the female group between 55 and 74 years of age (OR = 1.77, with a 95% confidence interval, 1.20–2.63, p = 0.001) resulted in worse functional outcomes.

In Rooij's cohort, when analyzing the risk of late cerebral ischemia according to age, a clear increase in risk for younger patients can be noted. Stratified by the WFNS scale and by the modified Fisher scale, only 3 of the 16 subgroups were at high risk (above 40%) for late-onset cerebral ischemia in the group of patients older than 55 years, while in those under 55 they were 5 out of 16 subgroups. In the same way, only 1 subgroup had a low risk (below 20%) in patients younger than 55 years, while 5 subgroups were considered low risk for age 55 years or older.

When we evaluated the grade 1 modified Fisher group, the mean difference was 5%. In these, when WFNS grade I, we found only a 3% increase in risk in the young group, from 12 to 15%. If WFNS II or III, the risk rises from 15 to 20%. Same difference was found in WFNS IV. When we have a WFNS V patient, the risk is 7% higher in the modified Fisher grade 1 patient if he is younger than 55 years.

For modified Fisher grade 2 patients, the mean risk for younger patients was 6.3% greater. If WFNS grade I, the risk is 5% higher in the under 55 age group. If the patient was WFNS II or III, the risk would rise from 22 to 28%. In WFNS grade IV, the difference rises from 24 to 30% in the under 55 age group. The greatest difference found was in patients younger than 55 years old WFNS V, where the increase was 8% in the risk of late cerebral ischemia compared to patients aged 55 years or older.

The same pattern was maintained in grade 3 patients on the modified Fisher scale. When WFNS I, increase of 5 percentage points, from 19 to 24% patients under 55 years old. In WFNS II or III patients, the risk rises by 6%. As for WFNS IV and V, we have a high risk of 7 and 8% respectively. So, the modified Fisher 2 patient has an average 6.5% greater risk of late cerebral ischemia if he has not reached the age of 55 years.

When we analyzed modified Fisher grade 4 patients, we found the greatest mean difference between the groups separated by age, where those younger than 55 years had a 7% higher risk of late cerebral ischemia. When WFNS grade I, 6% more; grade II or III, a significant 8% increase in risk, from 33% if aged 55 years or older to 41% if younger than 55 years.

For WFNS grade IV patients, the risk rises by 7% in younger patients. And, finally, modified Fisher 4 with WFNS grade V also presents a 7% increase in risk: 54 for an impressive 61% risk of late cerebral ischemia.

Discussion

In the selected studies, patients with aSAH below 55 years old have different clinical evolution. Lai(15) showed a high rate of angiographic vasospasm in women younger than 55 years, and, even though the objective of this study was to evaluate the female sex factor, its classification into subgroups with an evaluation of the age factor contributes to our research by relating the higher rate of vasospasm and a worse clinical outcome in this subgroup.

In the largest cohort among the selected studies, Oppong(16) defined age as an independent predictor for the occurrence of vasospasm. The reduced risk of vasospasm occurende is earlier in men, while for women it is evidenced later.

The mean risk of younger patients presenting late cerebral ischemia after aSAH is 6.2% higher in the study by de Rooij(10) in relation to the group over 55 years old. There is also evidence that the risk of late cerebral ischemia is higher in patients with higher modified Fisher grades, as previously mentioned in the study by Claasen(14), and in patients with more severe classifications on the WFNS scale.

Our review showed that patients under 55 years of age have differences in clinical evolution compared to older patients. It is important to assess such differences because aSAH is the cerebrovascular event with the greatest impact on young adults,(7) with consequences ranging from mild to severe neurological disability. In young adults, the socioeconomic implications of aSAH are also important, as they reduce potentially productive years in a population with a high life expectancy.(3) The main limitation of our study was the low number of studies that evaluated late cerebral ischemia according to different ages.

Conclusion

This bibliographical review highlights the importance of valuing younger age as a risk factor for the occurrence of angiographic vasospasm and late cerebral ischemia in patients with aSAH. Women are at a higher risk than men for these events, remaining high even after the age of 55, while in men the risk decreases.

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PRODUTO 2 – ARTIGO COORTE

World Neurosurgery

Analysis of delayed cerebral ischemia incidence after treatment for aneurysmal subarachnoid hemorrhage in young adults: a cohort study

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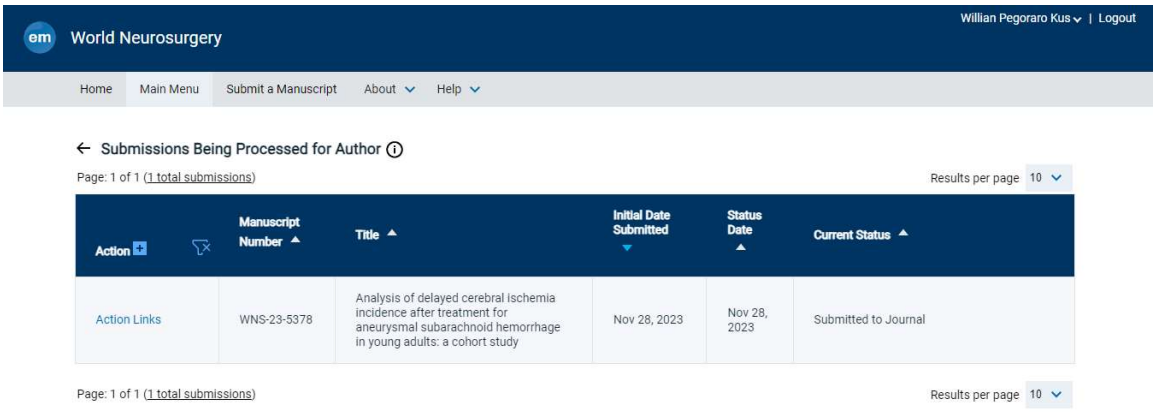

Title: Analysis of delayed cerebral ischemia incidence after treatment for aneurysmal subarachnoid hemorrhage in young adults: a cohort study

Short Title: Analysis of cerebral ischemia after SAH

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The authors confirm contribution to the paper as follows:
Study conception and design, writing the article, data collection, analysis and interpretation of results, and manuscript preparation: WPK; Data collection and analysis: FPF, YF, RC, VALJ; Discussion of the article and co-supervisor: LK;
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Abstract

Objective: To analyze the incidence of delayed cerebral ischemia (DCI) and outcome stratified by age in patients who suffered aneurysmal subarachnoid hemorrhage. **Methods:** Cohort study with patients from Christ The Redeemer Hospital from 2014 to 2020, with 359 patients separated into 2 groups, 48 of them aged under 40 years and 311 aged 40 years or over. **Results**: In patients under 40 years of age, delayed cerebral ischemia (DCI) was found in 81.3%, while in patients aged 40 or over it was 61.4%. A relative risk of 1.32 (CI: 1.12 to 1.55), with p = 0.013. After multivariate assessment, in patients aged under 40 years were found a 27 to 39% higher risk of presenting DCI. **Conclusions:** We identified that age under 40 years is a risk factor for the occurrence of DCI.

Keywords: Intracerebral aneurysm; Subarachnoid hemorrhage; Intracranial vasospasm; Cerebral ischemia.

Introduction

Non-traumatic subarachnoid hemorrhage (SAH) is a severe form of stroke characterized by abrupt arterial bleeding into the subarachnoid space. The cause in 80% of cases is the rupture of a brain aneurysm. The general lethality rate of

aneurysmal SAH (aSAH) is 32 to 67%.[1] Furthermore, approximately 30% of survivors will have moderate or severe disability.[2]

The incidence of SAH is controversial and variable in the world literature. Japan has an incidence of 22.7 cases per 100 thousand inhabitants per year, Finland records 19.7. In South and Central America, 4.2 cases per 100 thousand inhabitants per year. Such discrepancies are not only due to ethnic differences, but also to the variable degree of efficiency of health and surveillance systems, which can result in diagnostic error and underreporting. According to estimates, women are 1.24 times more likely than men. This difference only occurs from the sixth decade. In general, the etiological factors of aSAH in middle-aged and older adults patients, such as high blood pressure, are not common in patients under 40 years of age.[3,4]

Furthermore, the rate of aneurysmal rupture increases with age,[5] with a peak incidence between the fifth and sixth decade of life.[6] Therefore, the occurrence of aSAH in patients under 40 years old is uncommon. However, it is the form of stroke with the greatest impact on young adults.[7] Neurological consequences can range from mild cognitive decline to severe disability. In this age group, the pathology has important socioeconomic implications by reducing potentially productive years of a population with a high life expectancy.[3]

In general, the etiological and prognostic factors of aSAH in middle-aged and older adults patients are not common to patients aged under 40 years.[5,6]

Oppong[8] found the variable younger age as an independent predictor for the occurrence of vasospasm, OR = 1.03 per year of reduction with a 95% confidence interval, 1.01–1.05, and $p < 0.001$. Patients under 55 years of age had a significantly higher risk of vasospasm compared to older patients.

Research targeting this population is limited and scarce. Therefore, it is essential to direct our study to enhance public health policy measures that increase the quality of care for this population.

Therefore, the main objective of this study is to analyze the incidence of delayed cerebral ischemia (DCI) from aneurysmal SAH in adult patients up to 40 years of age, comparing those treated by microsurgery or endovascular surgery with patients in older age groups. Additionally, the study has two specific aims: 1) to assess the radiological outcome based on the rate of delayed cerebral ischemia resulting from vasospasm after aneurysmal rupture, and 2) to analyze the rate of return to work in discharged patients. This research aims to enhance our understanding of this disease, facilitating the development of public policies for the inclusion of this population.

Theoretical Reference

Anatomy of the Central Nervous System

The central nervous system (CNS) is entirely covered by membranes called meninges. In oder to evaluate their characteristics, they were separated into dura mater, arachnoid and pia mater.[9]

Externally there is the dura mater, thicker, rich in collagen fibers and well vascularized. In the brain, the main artery that supplies the dura mater is the middle meningeal artery, a branch of the maxillary artery. It is also richly innervated, unlike the other meningeal layers. Basically, intracranial sensitivity is located in the dura mater, as the brain parenchyma does not have sensitive nerve endings, which is responsible for headaches.[9]

The arachnoid is a delicate membrane that is located between the dura mater and the pia mater, constituting the subarachnoid space (Figure 1), responsible for housing the cerebrospinal fluid (CSF). In addition, there are delicate trabeculae called arachnoid trabeculae in the subarachnoid space, name derives from its appearance that resembles a spider's web.[9]

INSERT FIGURE 1

This space is compartmentalized into areas of dilation, forming areas with greater CSF quantity called subarachnoid cisterns, which provide the main surgical

site in neurosurgical interventions to approach aneurysms. The cisternal areas of the subarachnoid space consist of a more pronounced separation between the arachnoid mater and pia mater meninges, containing arachnoid trabeculae with CSF, cranial nerves and the intense vascular network of the brain.[9]

The cisterns are fundamental in the circulation of CSF throughout the brain. Firstly, CSF is produced within the lateral ventricles in the choroid plexuses, then descends through the foramen of Monro to the third ventricle, crosses the cerebral aqueduct and enters the fourth ventricle, from where, through openings called foramen of Luschka, laterally, and from Magendie, medially, gains the subarachnoid space bathing the brain stem, cerebellum, brain and other brain structures, in addition to the spinal cord and roots of the cauda equina in the lumbosacral spine. The main subarachnoid cisterns are the following: Ambient Cistern; Callous Cistern; Carotid Cistern; Chiasmatic Cistern; Crural Cistern; Interpeduncular Cistern; Lateral Cerebelomedullary Cistern; Terminal Blade Cistern; Magna Cistern; Olfactory Cistern; Prepontine Cistern; Quadrigeminal Cistern; Silvian Cistern.[10]

Sometimes the separation of these cisterns is based on purely anatomical criteria, given that the spaces are distributed continuously and there is not always a structure separating them, typically named after related structures. The intercommunication between the cisterns also drains the CSF until it is reabsorbed by the arachnoid granulations, mainly in the superior sagittal sinus, with the internal jugular vein as the main outlet, but also the cervicofacial lymphatic network. Involving the arterial structures, in addition to the subarachnoid space, invaginations of the subpial space form a covering sheath over the arteries, a structure called the Virchow-Robin space. The subarachnoid dissection method opens and connects these cisterns on the way to an aneurysm, for example.[10]

Knowledge of cerebral vascularization is essential to understand the damage resulting from vascular events. The cerebral vascularization initially originates from the aortic arch, where at the level of the sternoclavicular joint the first and largest of its branches, the right brachiocephalic artery, bifurcates into 2 terminal branches: the right subclavian artery and the right common carotid artery, while the left carotid artery originates directly from the apex of the aortic arch, immediately distal to the origin of the brachiocephalic artery. Bilaterally, both common carotid arteries bifurcate, approximately at the level of C5, into external carotid arteries, responsible for the vascularization of most head structures, excluding the brain and orbital

elements, and internal carotid arteries (ICA). These, in turn, are primarily divided according to Bouthillier into seven segments, namely: cervical, petrous, lacerum, cavernous, clinoid, ophthalmic and communicating. Just below the anterior perforated substance, the ICA bifurcates into the larger middle cerebral artery (MCA) and the anterior cerebral artery (ACA), half the diameter.[11]

The ACA is divided into 5 segments, with A1 and A2 being the proximal segments, while, from A3 onwards, the distal segments. There is also an artery called the anterior communicating artery (ACoA) that connects each of the anterior cerebral arteries, communicating at the level of A1-A2 both sides of the carotid arterial system. The MCA has 4 segments: horizontal (M1), insular (M2), opercular (M3) and cortical branches (M4).[11]

Branches of the subclavian arteries, the vertebral arteries (VA), one on each side, ascend through the spinal column through the transverse foramen to the posterior fossa, at the base of the skull, where they join to form the basilar artery (BA). Still in the posterior fossa, 3 arteries divide the territory to be nourished: superior cerebelar (SCA), or posteroinferior cerebellar (PICA) and, anteroinferior cerebellar (AICA). The BA ascends and bifurcates into the right and posteroinferior cerebral arteries (PICA). The PICA can be divided into 5 segments: pre-communicating (P1), post-communicating (P2), quadrigeminal (P3), cortical (P4) and terminal branches (P5).[11]

The posterior communicating artery (PCoA) originates in the posterior portion of the communicating segment of the ICA and anastomoses with the posterior cerebral artery (PICA), thus connecting the anterior to the posterior circulation. The set that arises from this union is called the Willis Polygon, the main structure of cerebral vascularization.[11]

Vascular events

A cerebrovascular accident (CVA) occurs when there is an acute and spontaneous change in cerebral blood flow, capable of causing loss of brain parenchyma and thus neurological damage. Classified according to their etiology as ischemic or hemorrhagic.[12]

Ischemic stroke is responsible for 80 to 85% of stroke cases, caused by interruption of flow in a cerebral artery due to embolism or thrombosis. Hemorrhagic

stroke occurs due to the leakage of arterial blood to the outside of the vascular structure, generating an increase in intracranial pressure and a deficit in blood flow even in areas not directly affected by the hematoma.[13]

There are three types of hemorrhagic stroke: 1) Intracerebral hemorrhage (ICH), also called intraparenchymal hematoma, may originate from damage to small penetrating arteries caused by systemic arterial hypertension or amyloid angiopathy. Or it may be secondary to a pre-existing injury, such as arteriovenous malformations; 2) Intraventricular hemorrhage, which alone is an important cause of bleeding in the neonatal phase, especially in premature babies. It may also occur concomitantly with subarachnoid hemorrhage or periventricular ICH with ependymal involvement and extravasation into the ventricular system; 3) Subarachnoid hemorrhage (SAH), representing only 5% of strokes, but its mortality in the acute and subacute phase can reach 50%.[14]

By definition, hemorrhagic stroke has a non-traumatic origin. Traumatic hemorrhages, such as epidural hematomas, subdural hematomas, traumatic subarachnoid hemorrhage (ATHS), even with the potential to generate neurological damage, are not classified as stroke, typically associated with acute or subacute trauma. If we refer to all SAH, the traumatic one is the majority in frequency. However, when referring generically to the SAH event, as with other hemorrhagic strokes, it is a non-traumatic SAH.[14]

In SAH, in 80% of rupture of aneurysms cases is the cause of bleeding, which is called aneurysmal SAH (aSAH). The incidence of SAH is controversial and variable in the world literature.[3,4]

Brain aneurysm

The cerebral vascular system is made up of distinct vascular structures. While the artery carries blood rich in oxygen and glucose to the brain tissue and other structures that surround it, the veins and venous sinuses are responsible for sending venous blood, poor in oxygen but rich in carbon dioxide and metabolites, back to the heart.

The healthy intracranial artery is made up of 3 layers, intima, media and adventitia. Internally, the intima forms the arterial lumen by a simple layer of endothelial cells followed by a membrane of elastic fibers, called the internal elastic

lamina. The middle layer has smooth muscle fibers and type III collagen. Externally, the adventitia is made up of type I collagen, elastin, fibroblasts and small nutrition vessels for this thick wall called vasa vasorum. Extracranial arteries still have an external elastic layer located between the media and adventitia layers.[14]

The formation of a cerebral aneurysm is associated with hemodynamic stress, when high shear forces act on the arterial wall, resulting in rupture of the internal elastic lamina, structurally weakening this wall. In response to the stress suffered, an adaptive process called myointimal hyperplasia occurs, with thickening of the wall, changes evident in unruptured aneurysms.[14]

When the aneurysm does not rupture in this initial phase, where the lesion is growing, at a certain point there will be a reduction in the shear force exerted on the wall, with hypoflow and an increase in the contact time between the blood and the injured endothelium, then developing an inflammatory reaction responsible for remodeling and further growth of the aneurysm. At this stage, atherosclerotic plaques may also form.[14]

The weakening of the wall is enhanced by the action of the inflammatory infiltrate and proteases that degrade the extracellular matrix, a complex network of proteins and proteoglycans synthesized by local cells and responsible for arterial structural support. Among the main proteases are metalloproteinases 2 and 9, which degrade elastin and collagen. Apoptotic cells are infrequent in the healthy arterial wall, but are frequently found in ruptured aneurysms, in greater quantities close to the rupture site, in addition to macrophages, T and B cells, immunoglobulins and activated complemente.[14]

Regarding the location of aneurysms, data from ISUIA[15], with 4.600 individuals with unruptured aneurysms, the internal carotid artery was the most frequent location (29.9%), excluding cavernous segment and PCoA. ACM presented 29.1% of injuries, ACoA 12.3% and PCoA only 8.5%.

On the other hand, Forget[16] found the position with the highest frequency of rupture in ACoA, with 29%. In second place is PCoA, with 19%, followed by ACM, with 11%. This pattern was also evidenced by other studies, such as ISAT.[17]

Complications of SAH

Two special situations contribute to SAH-related morbidity and mortality, early brain injury and cerebral vasospasm.[18] Early brain injury is considered to be one that occurs within 72 hours of aneurysmal rupture and is caused by an acute increase in intracranial pressure with decreased cerebral blood flow, with consequent cerebral edema and inflammation.

SAH can also cause cerebral vasospasm, a transient and self-limited narrowing of arterial vessels. This phenomenon is associated with delayed cerebral ischemia (TSI).[18] In these cases, in addition to the volume of bleeding, the location of the aneurysm can change the intensity of subsequent events. The more proximal the arteries reached by extra-luminal blood, the larger their caliber, so more distal vessels may be affected by hypoperfusion. Consequently, more regions will be at risk of ischemia and, thus, greater chances of neurological sequelae.

The period for its appearance usually begins 3 days after SAH, with a peak incidence on days 6 and 8 and can last for 2 to 3 weeks. There is a strong association with clinical decline caused by delayed cerebral ischemia in 20 to 30% of cases.[14]

Pathophysiology of vasospasm

Cerebral blood flow is affected by SAH through vasospasm, increasing cerebrovascular resistance and affecting autoregulation, increasing susceptibility with transient reductions in cerebral perfusion pressure with risk of hypoflow and ischemia.[20]

The regulation of the tone of vascular smooth muscle cells by actin and myosin filaments is carried out by the intracellular calcium reservoir. Calcium can have two main sources, the influx from the extracellular environment, regulated by calcium channels in the membrane, or calcium can be released by the sarcoplasmic reticulum through an increase in inositol 1,4,5-trisphosphate or the activation of sensitive receptors to ryanodine.[100]

Cyclic guanosine monophosphate (cGMP) acts on the sarcoplasmic membrane, activating calcium pumps and removing calcium, causing relaxation of smooth muscle cells. Nitric oxide (NO) is the main activator of cGMP that produces guanylate cyclase (GC).[20]

SAH affects cerebral blood flow mainly through endothelial mechanisms. There is evidence of impairment in endothelium-dependent relaxation, increased production of constricting factors derived from the endothelium and impaired activity of potassium channels.[20]

The main blood components responsible for compromising the endothelium are oxyhemoglobin and bilirubin, with oxyhemoglobin also eliminating NO, inactivating GC and increasing the production of free oxygen radicals.[20]

After being eliminated from endothelial cells, ON diffuses to smooth muscle cells and activates GC, which produces cGMP. This is responsible for activating intracellular calcium pumps, sequestering free calcium in intracellular reserves causing smooth muscle relaxation. Elimination of ON results in a reduction in GC activity, causing vasospasm.[20]

Still in the context of SAH, ferrous compounds such as hemoglobin produce oxygen free radicals and cause vasospasm, damaging endothelial and smooth muscle cells, increasing endothelial permeability and altering intracellular levels of calcium and inositol 1,4,5-trisphosphate.[20]

Depolarized smooth muscle cells were also observed after SAH, due to energy exhaustion or inhibition of potassium channels, generating membrane depolarization and then vasoconstriction.[20]

In this context, vasospasm and ICT are two important mechanisms for establishing brain injury after aneurysmal subarachnoid hemorrhage.

Material and Methods

A literature review was performed to analyze delayed cerebral ischemia after aSAH from the perspective of the patients' age. In the Pubmed/Medline, Lilacs, Epistemonikos, *Biblioteca Virtual e Saúde (VHL)* and Scielo databases, the search was performed using the descriptors: 1. Subarachnoid hemorrhage, 2. Cerebral ischemia, 3. Intracerebral aneurysm and 4. Age.

Articles published more than 10 years ago and those without analysis by age were discarded. There was no language limit. The initial selection obtained 167 articles and, subsequently, another 2 were included based on citations in the references of the selected articles. Of these 169 articles, 3 met the inclusion criteria and were analyzed.

Cohort

A retrospective cohort study was performed following the STROBE method with patients from a reference service in vascular neurosurgery in the state of Rio Grande do Sul, Christ The Redeemer Hospital (*Hospital Cristo Redentor*), in Porto Alegre, Brazil.

Using the Power and Sample Size for Health Researchers online version tool, we calculated a sample size of 148 subjects to test whether there is a difference between the percentages of delayed cerebral ischemia in the groups aged 18 to 40 years and over 60 years. Considering an increase of 10% for possible losses and refusals, this number was adjusted to 166. For the calculation, we considered a significance level of 5%, a percentage of 30%, a power of 80% and a relative risk of 1.8.[10]

The research structure was built under the acronym PICO:

Population: Patients with aneurysmal SAH treated by embolization or microsurgery.

Intervention: Patients with aneurysmal SAH treated by embolization or microsurgery, adults under 40 years of age.

Comparison: Patients with aneurysmal SAH treated by embolization or microsurgery, adults aged 40 years or older.

Outcome: Rate of delayed cerebral ischemia and return to work activities.

Initially, all patients admitted to Christ The Redeemer Hospital from January 1, 2014 to December 31, 2020 were selected, totaling 43.738 patients. Those patients admitted to the neurosurgery team within the same period were selected, 11.963 patients. Of those, 800 patients were selected and had one of the following ICDs recorded on the list of possible diagnoses at the time of admission or during hospital follow-up:

- I60.0: Subarachnoid hemorrhage from the siphon and carotid bifurcation;
- I60.1: Subarachnoid hemorrhage originating from the middle cerebral artery;
- I60.2: Subarachnoid hemorrhage from the anterior communicating artery;
- I60.3: Subarachnoid hemorrhage from the posterior communicating artery;
- I60.4: Subarachnoid hemorrhage originating from the basilar artery;
- I60.5: Subarachnoid hemorrhage originating from the vertebral artery;

- I60.6: Subarachnoid hemorrhage originating from other intracranial arteries;
- I60.7: Subarachnoid hemorrhage from an unspecified intracranial artery;
- I60.8: Other subarachnoid hemorrhages;
- I60.9: Unspecified subarachnoid hemorrhage.

The medical records of these 800 patients were analyzed and only patients with: a) SAH diagnosis confirmed, either through head CT or lumbar puncture; b) Confirmation of the aneurysmal etiology of SAH performed using tomography angiography of the cerebral vessels (CT Angio) or cerebral angiography; c) Microsurgical or endovascular treatment for the aneurysm(s).

Of the 365 eligible patients, 6 were excluded from the sample for not undergo a control CT scan after the critical period of vasospasm, within 3 weeks after the bleeding event, in order not to underestimate the incidence of ICT. Furthermore, ischemia resulting from complications of surgical clipping, endovascular embolization or occurring in the path of external ventricular shunt passage was disregarded.

At the end of applying the election criteria, 359 patients were elected and separated into 2 groups, 48 of them under 40 years of age and 311 aged 40 years or over.

The collection of demographic, epidemiological and clinical data occurred through review of medical records, imaging exams (CT, CT angiography and arteriograms) and telephone interviews. The informed consent form were presented to the participants. No patient dropped out during the study.

The following variables were collected: age, sex, previous comorbidities, history of smoking or alcohol consumption, family history of aneurysm, day of bleeding with interval until intervention(s), topography of the aneurysm, size (domus and neck) and aneurysm morphology, need for ventricular shunt, clinical picture on admission (Hunt & Hess), bleeding on initial CT (modified Fisher and Fisher), occurrence of intraoperative and postoperative complications, delayed cerebral ischemia, outcome (GOS), index and return to work and application of the SF-12 questionnaire.

Statistical analysis

Statistical processing of the data was performed using the Statistical Package for the Social Sciences, version 20.0. Comparison between groups (with and without

ICT) was performed using Pearson's chi-square test. The relationship between age and DCI was adjusted for HH, F and Fm using Poisson multiple regression with robust variance adjustment. It was necessary to perform 3 different models, due to the multicollinearity presented by the 3 severity scores, verified through the variance inflation factor (VIF) index. The significance level adopted is $p < 0.05$.

Ethical procedures

Considering the physical, psychological, moral, intellectual, social and cultural dimensions of the research participants, the study respected the guidelines and criteria established in Resolution 466/2012 of the National Health Council (BRASIL, 2013), ensuring the legitimacy of the information, privacy and confidentiality, according to the guidelines of the General Law for the Protection of Personal Data - Law No. 13.709 of August 14, 2018 (BRASIL, 2019), considering ethical precepts throughout the process of constructing the work and publishing the results.

Clarifications and guidance regarding the purpose of the research, as well as authorization from the patient or family member to participate, were provided via telephone.

This project was approved under CAAE number 63666422.2.0000.5530, approval opinion number 6.257.784 of August 24, 2023.

Results

Integrative Review

In Lai's cohort,[21] with 328 patients, the assessment using the age criterion had a cutoff point of 55 years. In this case, women in the subgroup under 55 years of age had a higher rate of angiographic vasospasm ($\beta = 0.56$; 95% confidence interval, 0.19 - 0.93; $p = 0.003$).

For Oppong,[16] in a cohort of 994 patients, younger age was an independent predictor for the occurrence of vasospasm, OR = 1.03 per year of reduction with 95% confidence interval, 1.01–1.05, and $p < 0.001$. When separated into 2 groups, patients under 55 years of age had a significantly higher risk of vasospasm compared to older patients. Women had OR = 1.84 with a 95% confidence interval,

1.28 - 2.67, and p = 0.001, while men had OR = 2.63; with 95% confidence interval; 1.38 - 5.01, and p = 0.003.

On the other hand, when these patients were separated into 3 groups (under 55 years old, 55 to 74 years old and over 74 years old), this study demonstrated an interesting relationship between vasospasm and the female sex factor. While in men the risk of high vasospasm in the younger group decreased in the second age group, between 55 and 74 years old, with this risk remaining low in the third, in women the high risk in the young group remained high in the intermediate group and was only reduced in the group of people over 74 years old. Furthermore, women aged 55 to 74 years had an increased risk of delayed cerebral ischemia, OR = 1.77, with 95% confidence interval, 1.20–2.63, p = 0.001, resulting in worsening of functional outcome of these patients.

Analyzing the probability of delayed cerebral ischemia found in de Rooij's cohort,[19] with 626 patients, using the age factor, the evident increase in risk for younger patients can be noted. Stratified by the WFNS scale from a clinical point of view and by the modified Fisher scale regarding the magnitude of bleeding, only 3 of the 16 subgroups presented a high risk (above 40%) for delayed cerebral ischemia in the group of patients aged 55 years or older, while in those under 55 years of age there were 5 of 16 subgroups. Likewise, only 1 subgroup presented low risk (below 20%) in patients under 55 years of age, while 5 subgroups were considered low risk for those aged 55 years or older.

When we evaluate the modified Fisher grade 1 group, the average difference is 5%. In these, when WFNS grade I, we found only a 3% increase in risk in the young group, from 12 to 15%. If WFNS II or III, the risk increases from 15 to 20%. Same difference found in WFNS IV. When we have a WFNS V patient, the risk is 7% higher in modified Fisher grade 1 patients if they are under 55 years old.

For modified Fisher grade 2 patients, 6.3% higher is the average risk for younger patients. If WFNS I, the risk is 5% higher in the under 55 group. If the patient had WFNS II or III, the risk would increase from 22 to 28%. In WFNS grade IV, the difference increases from 24 to 30% in the group under 55 years of age. The biggest difference found was in patients under 55 years of age in WFNS V, where there was an 8% increase in the risk of delayed cerebral ischemia in relation to patients aged 55 years or over.

The same pattern was maintained in grade 3 patients on the modified Fisher

scale. When WFNS I, increase of 5 percentage points, from 19 to 24% in children under 55 years of age. In WFNS II or III patients, the risk increases by 6%. For WFNS IV and V we have a high risk of 7 and 8% respectively. Therefore, the modified Fisher 2 patient has an average of 6.5% greater risk of delayed cerebral ischemia if he has not reached the age of 55 years.

When we analyzed modified Fisher grade 4 patients, we found the largest mean difference between the groups separated by age, where those under 55 years of age have a 7% higher risk of delayed cerebral ischemia. When WFNS grade I, 6% more; grade II or III, a significant 8% increase in risk, from 33% if aged 55 or over to 41% if under 55. For WFNS grade IV patients, the risk increases by 7 percentage points in younger patients. And, finally, modified Fisher 4 with WFNS grade V also presents a 7% increase in risk: 54 to 61% risk of delayed cerebral ischemia.

In the selected studies, patients with aSAH under 55 years of age present special characteristics of clinical evolution. Furthermore, Lai[21] showed a high rate of angiographic vasospasm in women under 55 years of age. Even though the objective of that study was to mainly evaluate the female sex factor, its classification into subgroups with evaluation of the age factor contributes to our research by relating the higher rate of vasospasm to a worse result in the clinical outcome score in this young subgroup.

In the largest cohort among the selected studies, Oppong[16] defined age as an independent predictor for the occurrence of vasospasm. The drop in the risk of its occurrence is earlier in men, while for women this effect is evident later.

The average risk of younger patients presenting delayed cerebral ischemia after aSAH is 6.2% higher in the study by de Rooij[19] compared to the group over 55 years of age. The risk of delayed cerebral ischemia is also evident, being higher in patients with high modified Fisher grades, as previously mentioned in the study by Claasen,[14] and in patients with more severe classification on the WFNS scale.

This review showed that patients under 55 years of age present differences in clinical evolution compared to older patients. It is important to evaluate such differences because aSAH is the form of stroke with the greatest impact on young adults,[7] with mild neurological consequences, such as cognitive decline, up to severe disability. In young adults, the socioeconomic implications of SAH are also important as they reduce potentially productive years of a population with a high

life expectancy.[3] There was the limitation of few studies addressing the analysis of the risk of delayed cerebral ischemia by age group.

Cohort

Selecting the 43.738 patients admitted to the Christ The Redeemer Hospital from 2014 to 2020, 11.963 were from the neurosurgery team. Of those, 800 patients presented SAH CID and were analyzed. A total of 365 patients were diagnosed with aSAH and received microsurgical or endovascular treatment. Patients who did not undergo a control CT scan after the critical period of vasospasm were excluded from the sample, which is why 359 patients were chosen and separated into 2 groups, 48 of them under 40 years of age and 311 aged 40 years or over, as shown in Figure 2.

INSERT FIGURE 2

Analyzing our population in terms of sex, there was a predominance of women in a ratio of 3:1, with 262 women (73.2%) and 96 men (26.8%). There was no statistically significant difference in relation to sex in the DCI index, being present in 64.6% of men and 64.1% of women. ($p = 0.932$)

Regarding comorbidities, arterial hypertension was most prevalent, present in 54.5% of patients, followed by diabetes mellitus (10.3%), psychiatric diseases (8.4%) and obesity (3.9%). None of these comorbidities demonstrated a statistically significant difference in the DCI index ($p > 0.05$).

We found a smoking rate of 59.7%, with 49.3% being active smokers and 10.4% ex-smokers. The DCI of those who never smoked was 67.6, while ex-smokers and smokers were 61.1 with $p = 0.26$, also demonstrating no statistical significance.

We found 8.7% of patients with a family history of aneurysms. Alcoholism was reported by 9.8% of patients. There was DCI in 77.1% of alcoholics compared to 62.8% of non-drinkers, but without statistical significance ($p = 0.135$). Data shown in Table 1.

INSERT TABLE 1

Most of our patients (54.5%) had their treatment, microsurgical or endovascular, within the fifth day after the rupture. In 67% of cases, a cerebrospinal fluid drainage system, EVD or VPD was used. CNS infections were diagnosed in 41.4% of cases.

Among the causes of death, sepsis emerged as the leading factor, accounting for 41.9% of cases, followed by brain death (39.5%), respiratory infections (11.6%), and multiple organ failure (4.7%). Regarding location, 38.3% of patients had aneurysms in the communicating segment of the internal carotid artery, PCoA, the most common in our sample, followed by the anterior communicating artery, ACoA, with 28.5%. The middle cerebral artery, ACM, was affected in 28.2% of cases, while the ophthalmic segment of the internal carotid artery was affected in 12.6%. Other locations of the anterior circulation presented aneurysms in 7.8% of patients. The basilar artery presented an aneurysm in 5.6% of patients and there was an aneurysm in other locations of the posterior circulation in 4.5% of patients (Figure 3).

INSERT FIGURE 3

The HH scale was used to classify patients with SAH according to their clinical condition. In our sample, we had 16.6% of patients with HH 1; 42.2% had HH 2; 28.2% were HH 3; 8.4% HH 4 and only 4.7% had an HH 5 classification.

Relating the HH variable with the DCI index in Graph 2, we evidence a significant association ($p = 0.013$). We also showed a statistically significant linear trend, the higher the classification, the higher the degree of DCI ($p = 0.015$).

INSERT FIGURE 4

Regarding the severity of bleeding, head CT scans are evaluated and classified using the Fisher and modified Fisher scales. Our sample highlights the close relationship between a higher Fisher and modified Fisher grade with a higher prevalence of DCI (Graph 3), both with $p < 0.001$ (chi-square test for linear trend).

INSERT FIGURE 5

Of the 48 patients under 40 years of age, 39 had ICT (81.3%). Of the 307 patients aged 40 or over, only 189 showed ICT (61.4%). In this group, ICT was present in 63.6% of patients between 40 and 60 years of age, while over 60 years of age it was present in 58.5% of patients. The relative risk of DCI in the group under 40 years old found in this sample was 1.32 (CI: 1.12 to 1.55), with a statistical significance of 0.013 (Table 2).

INSERT TABLE 2

We analyzed DCI according to the Hunt-Hess scale, separating it into 2 groups, HH 1 and 2 and HH 3 to 5, and Fisher's classification in a similar way. In the same way, we can evaluate the DCI index by stratifying according to the Hunt-Hess scale and the modified Fisher classification (Table 3).

INSERT TABLE 3

Three multivariate analysis models were carried out to clarify the independent relationship between the age variable and DCI, when adjusted for the HH, Fisher and modified Fisher scales individually, due to the multicollinearity between these indices (Table 4).

INSERT TABLE 4

The recovery of the graduates' work capacity was also assessed. In our study we found a higher frequency of recovery of economic activities in the group under 40 years old, where 50.0% reported returning to work in the same role, while between 40 and 60 and over 60 years old the value found was 18.5 and 13 .9% respectively.

Discussion

Analyzing our sample in terms of sex, there was a predominance of women at a frequency of 3:1, with 73.2% women and 26.8% men. Aneurysms predominate in females and this proportion is reported in the literature.[14]

Regarding comorbidities, systemic arterial hypertension (SAH) was more prevalent, present in 54.5% of patients. Chronically elevated blood pressure levels

are an important factor in the genesis of aneurysmal rupture. Prospective and retrospective studies show a 2.5 to 3.5 times greater chance of aneurysm rupture in patients with SAH.[14]

We found a smoking rate of 59.7%, with 49.3% being active smokers and 10.4% ex-smokers. The chance of aneurysmal rupture is 2 to 3 times greater than developing aSAH, reaching 6 times when there is a family history of ruptured cerebral aneurysm.[14] In our sample, 8.7% had a family history of aneurysms.

Regarding vasospasm, Lai[21] demonstrated a high rate of angiographic vasospasm in women under 55 years of age. Oppong[8] defined age as an independent predictor for the occurrence of vasospasm and reported a drop in the risk of its earlier occurrence in men, while for women this effect was evident later; however, in our sample there was no statistically significant difference in relation to sex in the DCI index, being present in 64.6% of men and 64.1% of women (p = 0.932).

Regarding the location of the aneurysms, our results present a slight difference in relation to the ISUIA[15] data, where the internal carotid artery was the most frequent location (29.9%), excluding the cavernous segment and PCoA. MCA presented 29.1% of injuries, similar to our result of 28.2%. At ACoA, ISUIA presented 12.3%, while we found 28.2%. The biggest difference was evident in PCoA, where ISUIA found only 8.5%, while our sample showed 38.3%. We emphasize that in that study we were dealing with unruptured aneurysms.

On the other hand, Forget[16] and ISAT[17] evaluated ruptured aneurysms. The frequency found by Forget at ACoA was 29%, close to our result of 28.5%. In second place in Forget's study, PCoA presented 19% of aneurysms, while this segment was the most frequently affected in our sample, with 38.3%. Finally, in third place in the Forget and ISAT studies, the MCA affected in 11% of Forget's cases was more frequent in our sample, at 28.2%.

When analyzing DCI stratified by age, in patients under 40 years of age, we found DCI in 81.3%, while in patients aged 40 or over it was 61.4%, making up a relative risk of DCI in the group under 40. years of 1.32 (CI: 1.12 to 1.55), with a statistical significance of 0.013 (Table 2).

This probability of increased DCI in young patients was reported in de Rooij's cohort[19], with 371 patients, where stratification was created using the WFNS and modified Fisher scale. In the group of patients aged 55 or over, only 3 of the 16

subgroups presented a high risk for delayed cerebral ischemia, 18.25%, while in those under 55 years of age, 5 of the 16 subgroups were at high risk, 31.25%. With the same stratification, for those aged 55 years or over, 31.25% were considered low risk, while in patients under 55 years of age, only 6.25% presented low risk (Table 5).

INSERT TABLE 5

In our cohort, we analyzed DCI according to the HH scale, separating it into 2 groups, HH 1 and 2 and HH 3 to 5, and the F classification in a similar way. Likewise, we evaluated the DCI index by stratifying according to the HH scale and the Fm classification.

It is observed that, in line with de Rooij's findings, elevated Hunt and Hess scores (HH), Fisher grades (F), or modified Fisher grades (Fm) serve as risk factors for the onset of intracranial hemorrhage-related complications. With a more refined evaluation of the age criterion within our cohort, being under 40 years old emerges as a significant standalone risk factor for the occurrence of end-stage renal disease (ESRD).

Table 4 presents the multivariate evaluation with statistical significance in any of the associations between age and the HH, F and Fm criteria, proving the importance of this variable as a risk factor for the occurrence of DCI. We concluded that age remained related to DCI even when adjusted, showing a risk that varies from 1.27 to 1.39, that is, at least, those patients under 40 years of age have a 27% higher risk of presenting DCI.

Study limitations

The initial limitation encountered in conducting this study is associated with the sample size of patients below the age of 40, as the incidence of aneurysmal rupture tends to increase with age, peaking in the fifth and sixth decades. [6] The data collection started in 2014, representing the earliest year documented in the CRH internal medical records system. Consequently, a comprehensive analysis was conducted, encompassing patients from this starting point until the year immediately preceding the initiation of the study.

Furthermore, the analysis based on the application of the SF-12 was of great value, but did not reach the expected values to consider statistical validity in comparative analyses, given the limitations found in making telephone contact with patients or family members.

Conclusion

With the data from this study, we identified age under 40 years as a risk factor for the occurrence of DCI, in addition to clinical (Hunt-Hess) or radiological (Modified Fisher or Fisher) condition at hospital admission.

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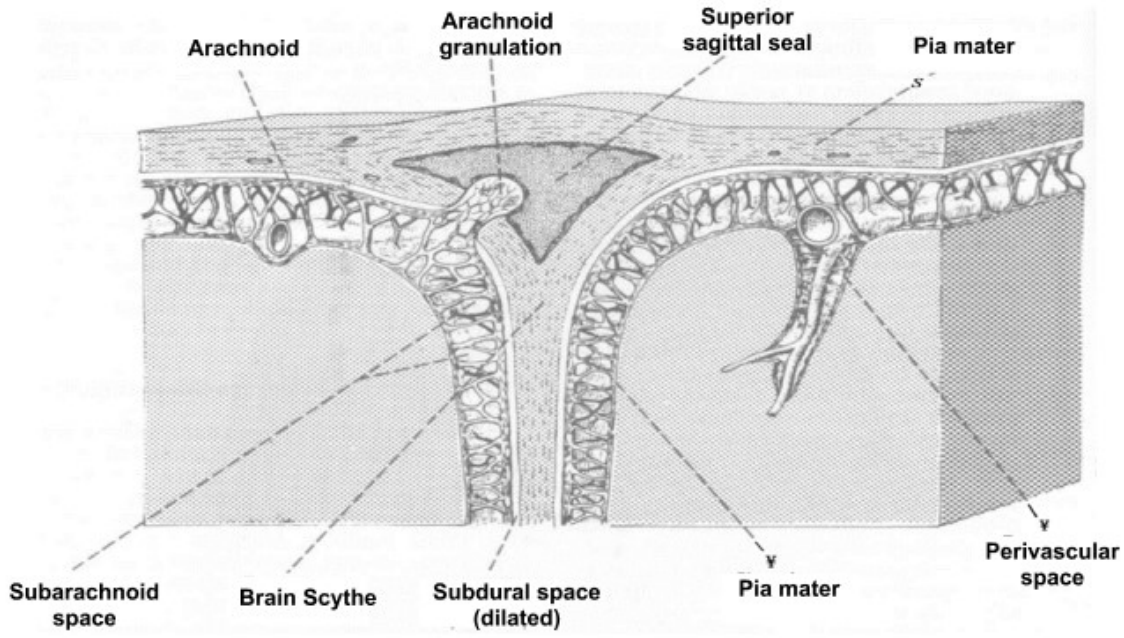
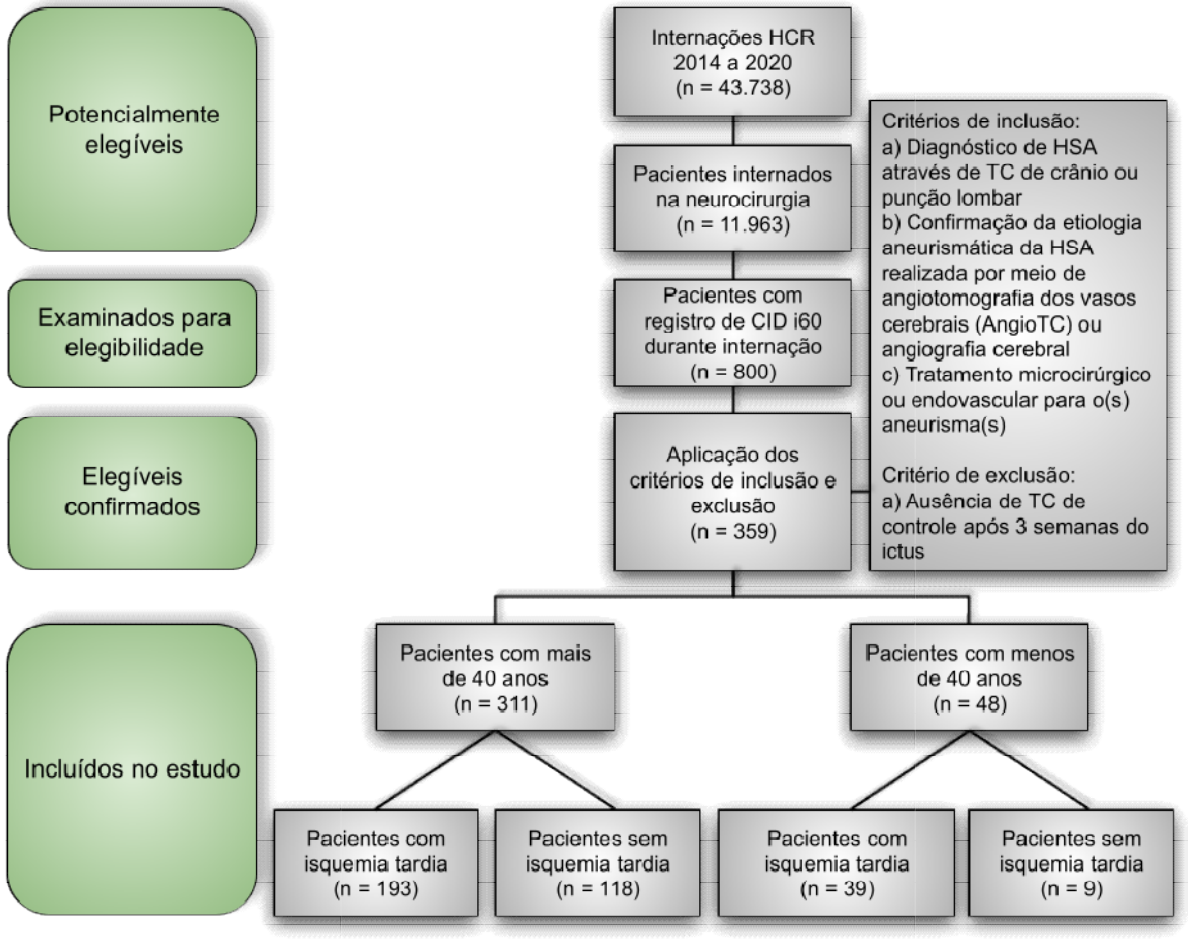
Figure Legends

Figure 1. Transverse section of the superior sagittal sinus showing the arachnoid granulation, the arrangement of the meninges and the meningeal spaces.



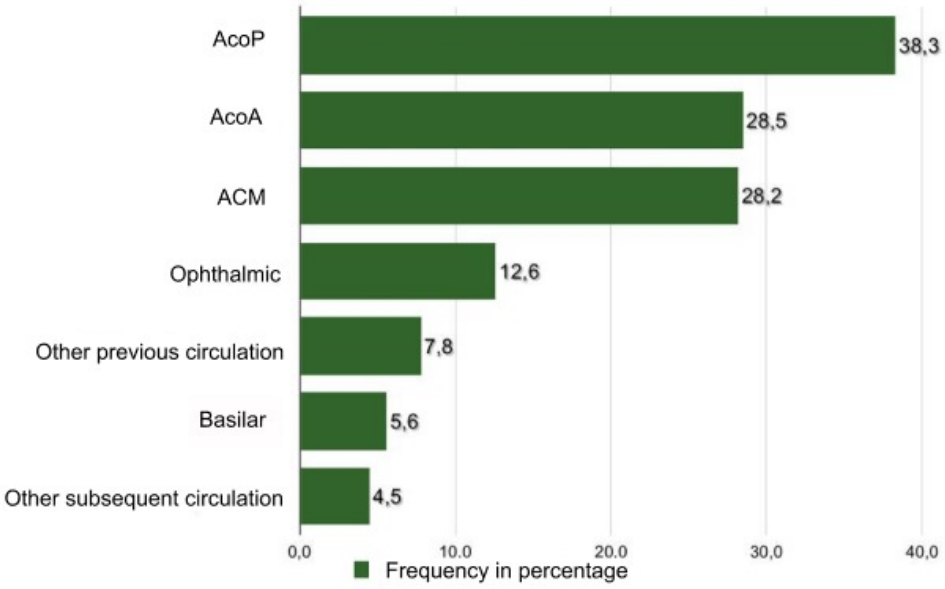
Source: Machado (2007).

Figure 2. Patient selection flowchart.



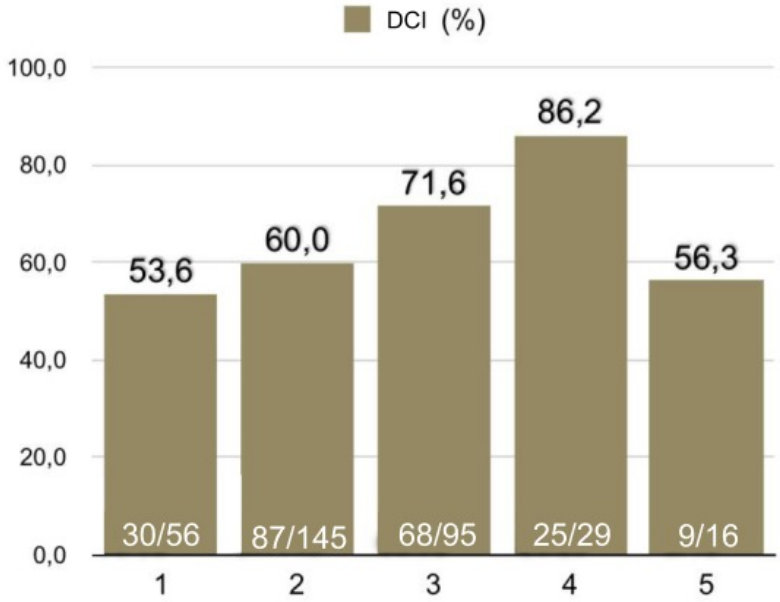
Source: Prepared by the author (2023).

Figure 3. Distribution of aneurysms by location.



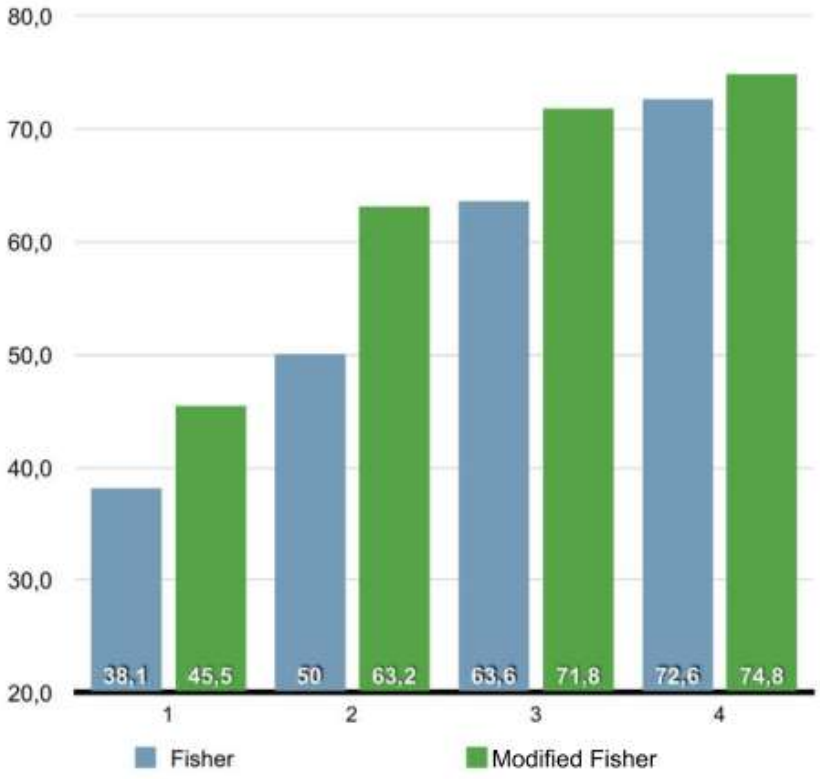
Source: Prepared by the author (2023).

Figure 4. Frequency of DCI according to the clinical classification of HH.



Source: Prepared by the author.
Note: DCI - Delayed Cerebral Ischemia.

Figure 5. DCI in percentage and degree of bleeding using the Fisher and modified Fisher scales (in percentage).



Source: Prepared by the author (2023).

Table 1. Sample characteristics.

Characteristics	
Sex	
Man	26.8%
Woman	73.2%
Age	
< 40 years old	13.4%
≥ 40 years old	86.6%
Arterial hypertension	54.5%
Diabetes mellitus	10.3%
Smoking	59.7%
Active	49.3%
Ex-smokers	10.4%
Alcoholism	9.8%
Family history of aneurysm	8.7%

Source: Prepared by the author (2023).

Table 2. Delayed Cerebral Ischemia (DCI) according to age.

Results			
DCI according to age			
< 40 years old	81.3%		RR 1.32 (CI: 1.12 - 1.55)
≥ 40 years old		61.4%	
40-60 incomplete years		63.6%	
≥ 60 years old		585%	

Source: Prepared by the author (2023).

Table 3. Prevalence of DCI by age according to the Hunt-Hess (HH) and Fisher (F) or modified Fisher (Fm) combination.

Results		
DCI in < 40 anos	F 1 and 2	F 3 and 4
HH 1 and 2	75.0%	75.0%
HH 3 to 5	-	100%
DCI in ≥ 40 anos	F 1 and 2	F 3 and 4
HH 1 and 2	39.1%	64.3%
HH 3 to 5	42.9	71.1%
DCI in < 40 anos	Fm 1 and 2	Fm 3 and 4
HH 1 and 2	68.8%	84.2%
HH 3 to 5	100%	100%
DCI in ≥ 40 anos	Fm 1 and 2	Fm 3 and 4
HH 1 and 2	43.9%	68.8%
HH 3 to 5	58.8%	72.6%

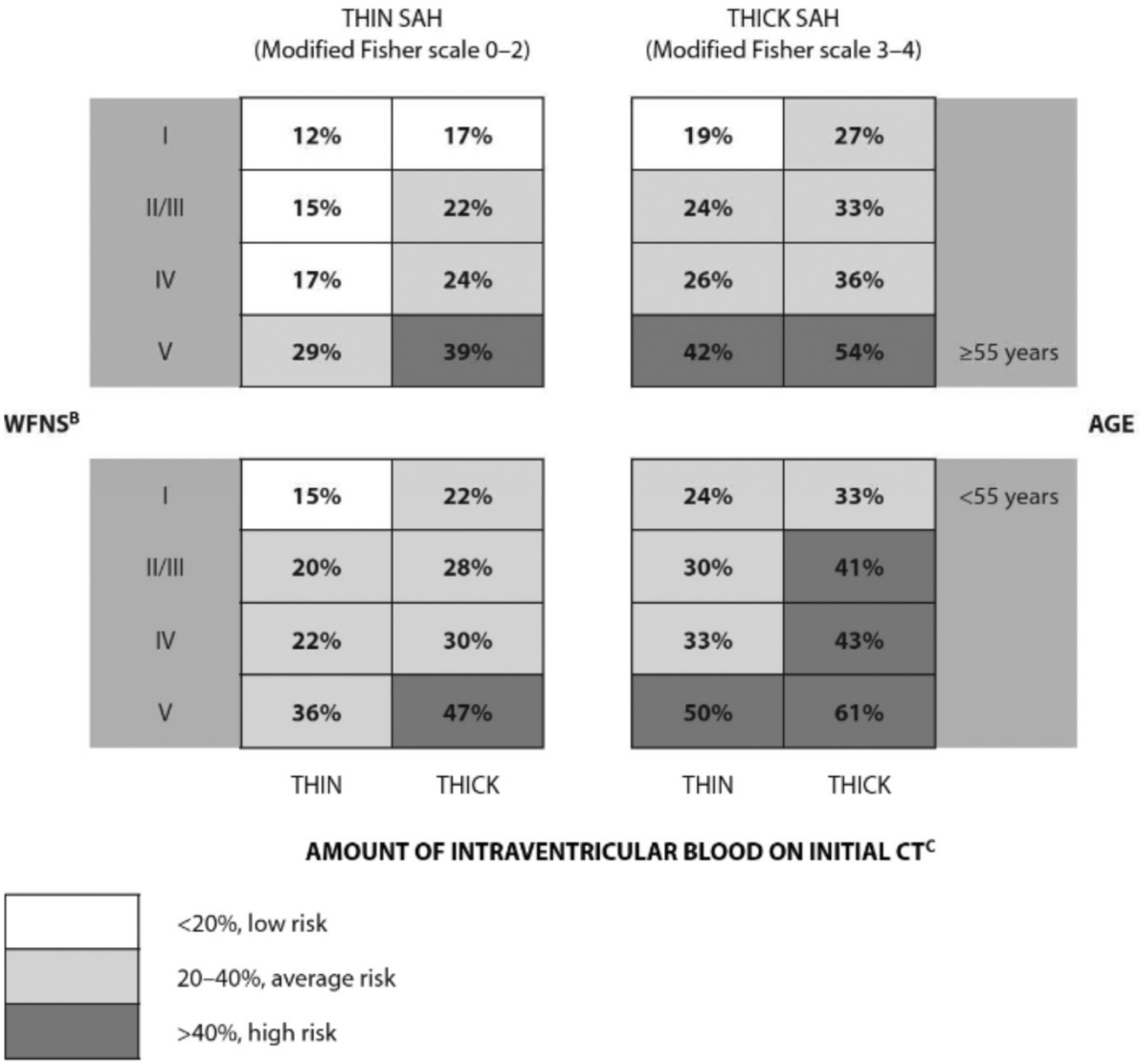
Source: Prepared by the author (2023).

Table 4. Multivariable analysis of age in relation to DCI, adjusted for severity indices (HH, F and Fm).

Multivariate analysis			
DCI as dependent variable			
	RR	CI (95%)	P
Age	1.391	1.185 - 1.632	< 0.001
Hunt-Hess	1.296	1.111 - 1.512	= 0.001
Age	1.277	1.085 - 1.503	= 0.003
Fisher	1.517	1.153 - 1.996	= 0.003
Age	1.328	1.135 - 1.554	< 0.001
Modified Fisher	1.437	1.178 - 1.753	< 0.001

Source: Prepared by the author (2023).

Table 5. Probability of DCI after SAH for each combination of the 4 main independent predictors present at admission.



Source: Rooij et al. (2013).

5 CONCLUSÕES E CONSIDERAÇÕES FINAIS

Não obstante o significativo desenvolvimento tecnológico da medicina, o tratamento dos pacientes com ruptura aneurismática intracerebral consiste num desafio para a equipe assistencial, por tratar-se de uma doença de prognóstico devastador, com potencial de morbimortalidade elevados.

Dentre as complicações com poder de acentuar as sequelas da HSAa, a mais relevante é a ICT. Com identificação por vezes confusa, apresentação tardia e limitações no diagnóstico, somada a reduzida janela de intervenção terapêutica, torna-se indispensável a identificação dos fatores de risco. Desta forma, permitimos tratar de forma agressiva pacientes com risco elevado antes de ocorrer um evento isquêmico irreversível.

Com os dados deste estudo, identificamos a idade abaixo de 40 anos como fator de risco para ocorrência de ICT, além de condição clínica (Hunt-Hess) ou radiológica (Fisher ou Fisher modificada) na admissão hospitalar.

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APÊNDICE E ANEXOS

A. APROVAÇÃO PELO COMITÊ DA ÉTICA E PESQUISA

HOSPITAL NOSSA SENHORA DA CONCEIÇÃO

GRUPO HOSPITALAR CONCEIÇÃO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Desfecho após tratamento de pacientes adultos jovens com hemorragia subaracnoide aneurismática

Pesquisador: Paulo Valdeci Worm

Versão: 4

CAAE: 63666422.2.0000.5530

Instituição Proponente:HOSPITAL CRISTO REDENTOR SOCIEDADE ANONIMA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 6.257.784

Apresentação do Projeto:

A hemorragia subaracnoide (HSA) não traumática é uma forma grave de acidente vascular encefálico, caracterizada por sangramento arterial abrupto no espaço subaracnoide. A causa em 80% dos casos é a ruptura de um aneurisma cerebral. A taxa de letalidade geral da HSA aneurismática (HSAa) é de 32 a 67%. Além disso, aproximadamente 30% dos sobreviventes apresentarão incapacidade moderada ou grave. A taxa de ruptura aneurismática aumenta com a idade, sendo que o pico de incidência ocorre entre a 5a e 6a década de vida. A ocorrência de HSAa em pacientes com menos de 40 anos é incomum. Entretanto, é a forma de acidente vascular encefálico de maior impacto em adultos jovens. As consequências neurológicas variam desde declínio cognitivo leve até quadros de incapacidade

severa. Neste grupo etário a patologia apresenta importantes implicações socioeconômicas por reduzir anos potencialmente produtivos de uma população com uma expectativa de vida alta. De maneira geral, os fatores etiológicos e prognósticos da HSAa em pacientes de meia-idade e idosos não são comuns aos pacientes com menos de 40 anos. Sendo assim, o objetivo desta pesquisa é analisar uma população de adultos jovens com hemorragia subaracnoide aneurismática de tratamento microcirúrgico e endovascular no serviço de referência para esta patologia no Rio Grande do Sul.

Objetivo da Pesquisa:

Analisar o desfecho da HSA em pacientes adultos jovens tratados por microcirurgia e embolização, comparado com pacientes de faixas de idade mais elevadas. Objetivo Secundário: Identificar possíveis fatores de risco para HSA neste subgrupo; Analisar o índice de vasoespasmo e consequências isquêmicas através de análises tomográficas; Analisar o desempenho cognitivo destes pacientes e potencias perdas de anos de vida ativa; Analisar a qualidade de vida através do questionário "Short Form Health Survey 12" (SF- 12), observando diferenças clínicas no estado de saúde dos pacientes; Averiguar o índice e retorno ao trabalho com finalidade de desenvolver políticas públicas de inclusão desta população.

Avaliação dos Riscos e Benefícios:

Riscos:
O estudo respeitará as diretrizes e critérios estabelecidos na Resolução 466/2012 do Conselho Nacional de Saúde (CNS), zelando pela legitimidade das informações, privacidade e sigilo, considerando os preceitos éticos em todo o processo de construção do trabalho e na divulgação dos resultados. São consideradas as dimensões física, psíquica, moral, intelectual, social e cultural dos integrantes da pesquisa, buscando precocemente identificar riscos de danos ao participante para minimizá-los antecipadamente.

Benefícios:
A divulgação do estudo contribuirá para a construção de conhecimento científico sobre o comportamento da HSA em pacientes jovens e para a construção de protocolos institucionais específicos.

Comentários e Considerações sobre a Pesquisa:

Será realizado estudo observacional retrospectivo no qual a coleta de dados será realizada após a aplicação dos critérios de inclusão e exclusão. Os integrantes desta pesquisa são pacientes oriundos de serviço referência em neurocirurgia vascular no estado do Rio Grande do Sul, Hospital Cristo Redentor/GHC. Por meio da ferramenta PSS Health versão on-line, foi calculado um tamanho de amostra de 148 sujeitos para testar se existe diferença entre os percentuais de isquemia cerebral tardia nos grupos adulto jovem, de 18 a 40 anos incompletos, e controle, acima de 60 anos. Considerando acréscimo de 10% para possíveis perdas e recusas, este número deve ser 166, 83 em cada grupo. Consideramos para o cálculo nível de significância de 5%, percentual de 30%, poder de 80% e risco relativo de 1.8. Serão incluídos pacientes internados entre Jan/14 e Dez/20 com diagnóstico de HSAa firmado através de TC de crânio e/ou punção lombar. A confirmação da etiologia aneurismática será realizada por meio de angiotomografia dos vasos cerebrais (AngioTC) e/ou angiografia cerebral. Através de revisão de prontuários e de exames de imagem (TC, angioTC e arteriografias), consultas ambulatoriais e entrevistas por telefone, realizaremos uma coleta de dados demográficos, epidemiológicos e clínicos dos egressos. As seguintes variáveis serão coletadas: idade, sexo, comorbidades prévias, história de tabagismo ou etilismo, história familiar de aneurisma, dia do sangramento com intervalo até a(s) intervenção(ões), topografia do aneurisma, tamanho (colo e domus) e morfologia do aneurisma, presença de DVE, quadro clínico na admissão (Hunt & Hess), sangramento na TC inicial (Fisher), ocorrência de complicações transoperatórias e pós-operatórias, isquemia cerebral tardia, desfecho (GOS) e índice e retorno ao trabalho. Os dados serão devidamente registrados em software de processamento de tabelas, no programa Excel (Microsoft).Os pacientes serão estratificados segundo idade, sexo, comorbidades prévias, história de tabagismo ou etilismo, história familiar de aneurisma, dia do sangramento com intervalo até a(s) intervenção(ões), topografia do aneurisma, tamanho (colo e domus) e morfologia do aneurisma, presença de DVE, quadro clínico na admissão (Hunt & Hess), sangramento na TC inicial (Fisher), ocorrência de complicações transoperatórias e pós-operatórias, isquemia cerebral tardia, desfecho (GOS) e índice e retorno ao trabalho. Os dados estatísticos serão analisados e comparados com a literatura atual disponível com finalidade de

identificar concordâncias e discrepâncias com a amostra estudada.O processamento estatístico dos dados será realizado pelo programa SPSS for Windows. A comparação entre os grupos será feita a partir do teste t de Student. O nível de significância adotado será de p<0,05. A normalidade da distribuição dos dados será realizada pelo teste de Kolmogorov-Smirnov. A análise de concordância entre os grupos será analisada com o teste de correlação de Spearman. A comparação das médias entre os grupos será realizada pelo teste de Tukey.

Considerações sobre os Termos de apresentação obrigatória:

Todos documentos obrigatórios apresentados.

Conclusões ou Pendências e Lista de Inadequações:

Diante do exposto, o Comitê de Ética em Pesquisa do Grupo Hospitalar Conceição manifesta-se pela aprovação do projeto de pesquisa. O pesquisador assume o compromisso de seguir a Resolução no 466 de 2012 do Conselho Nacional de Saúde que trata das diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos, e, as normativas éticas complementares vigentes.

Considerações Finais a critério do CEP:

Diante do exposto, o Comitê de Ética em Pesquisa do Grupo Hospitalar Conceição manifesta-se pela aprovação do projeto de pesquisa. O pesquisador assume o compromisso de seguir, a Resolução no 466 de 2012 do Conselho Nacional de Saúde que trata das diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos, e, as normativas éticas complementares vigentes.

Situação do Parecer: Aprovado

Necessita Apreciação da CONEP: Não

PORTO ALEGRE, 24 de Agosto de 2023

Assinado por:
TALITA GIACOMET DE CARVALHO

(Coordenador(a))

B. TCLE

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

(Autorização via gravação telefônica)

A partir desse momento essa ligação está sendo gravada e vou proceder o esclarecimento sobre a pesquisa. Você está sendo convidado a participar de uma pesquisa do Curso de Mestrado do Grupo Hospitalar Conceição - GHC, intitulada: “Desfecho após tratamento de pacientes adultos jovens com hemorragia subaracnóide aneurismática”, que tem como objetivo principal analisar o desfecho dos pacientes operados após um aneurisma cerebral ter se rompido, comparando pacientes adultos jovens com faixas de idade mais elevadas (Registro no CAAE número 63666422.2.0000.5530).

O tema escolhido se justifica pela importância de estudar como estão evoluindo os pacientes depois do tratamento cirúrgico, seja após a clipagem microcirúrgica ou a embolização por técnica endovascular, além de comparar com outras faixas de idade e poder avaliar nelas possíveis diferenças.

O trabalho está sendo realizado pelo mestrando Willian Pegoraro Kus e sob a supervisão e orientação do Dr. Paulo Worm, do serviço de neurocirurgia do Hospital Cristo Redentor/GHC.

Para alcançar os objetivos do estudo será realizada uma entrevista individual estruturada com duração aproximada de 15 minutos, na qual você irá responder perguntas sobre seu estado de saúde. Os dados de identificação serão confidenciais e os nomes reservados. Destaco que nesse estudo foram delimitados os Riscos e Benefícios sendo eles: zelar pela legitimidade das informações, privacidade e sigilo, considerando os preceitos éticos em todo o processo de construção do trabalho e na divulgação dos resultados, buscando precocemente identificar riscos de danos ao participante para minimizá-los antecipadamente e divulgar o estudo a fim de contribuir para a construção de conhecimento científico sobre o comportamento da HSA em pacientes jovens e para a construção de protocolos institucionais específicos.

Os dados obtidos serão utilizados somente para este estudo, sendo os mesmos armazenados pelo (a) pesquisador(a) principal durante 5 (cinco) anos e após serão totalmente destruídos (conforme preconiza a Resolução 466/12). Você

entendeu as informações sobre os objetivos e a importância desta pesquisa de forma clara? ___

Destaco também que você irá receber resposta a qualquer pergunta ou esclarecimento acerca dos assuntos relacionados a esta pesquisa; que a sua participação é voluntária e você tem a liberdade de retirar o seu consentimento a qualquer momento e deixar de participar do estudo, sem que isto traga prejuízo para a minha vida pessoal e nem para o atendimento na instituição; que você não será identificado quando da divulgação dos resultados e que as informações serão utilizadas somente para fins científicos do presente projeto de pesquisa.

Você entendeu essas últimas informações? ___

Qualquer dúvida sobre o projeto de pesquisa e a forma como está sendo conduzido ou novas perguntas você poderá entrar em contato com o pesquisador: Dr. Paulo Worm, serviço de neurocirurgia, telefone 51 3357 4100, e-mail: pauloworm@hotmail.com. Endereço: Rua Domingos Rubbo, 20, Bairro Cristo Redentor, Porto Alegre, das 7:00 às 12:00 e das 13:30 às 15:30;

Ou ainda, se houver dúvidas quanto a questões éticas, poderá entrar em contato com Daniela Montano Wilhelms, Coordenadora-geral do Comitê de Ética em Pesquisa do GHC pelo telefone 3357-2805 ou e-mail cep-ghc@ghc.com.br. Endereço: Av. Francisco Trein, 326, Porto Alegre. Centro de Educação Tecnológica e Pesquisa em Saúde – CETPS (ESCOLA TÉCNICA GHC), Gerência de Ensino e Pesquisa, das 8:00 às 12:00 e das 14:30 às 15:30.

Você concorda em fazer parte da pesquisa? ___

Neste momento a gravação está sendo encerrada e agradeço pela sua atenção.