UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE ODONTOLOGIA

BIANCA FERST BALBINOT

GRP78 É UM BOM BIOMARCADOR DE PROGNÓSTICO TUMORAL? UMA REVISÃO SISTEMÁTICA

Porto Alegre
2021

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Trabalho de Conclusão de Curso apresentado ao Curso de Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Cirurgiã-Dentista.

Orientador(a) : Profª. Drª. Fernanda Visioli

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Porto Alegre, 20 de Maio de 2021.

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AGRADECIMENTOS

Agradeço, primeiramente, a Deus, que sempre esteve presente iluminando meu caminho e me dando muita força durante essa longa trajetória da graduação.

Agradeço aos meus pais Clair e Jair e ao meu irmão Lucas, por todo o suporte, união, carinho, amor e preocupação comigo durante esses anos. Vocês sempre estiveram comigo durante os dias difíceis e nunca mediram esforços para me proporcionar tudo isso, e sem vocês nada seria possível. Sou extremamente grata e feliz por Deus ter me inserido nessa família.

Agradeço ao meu namorado Milton, por ter entrado na minha vida e ter feito toda a diferença durante esses anos. Ele viveu tudo comigo durante a graduação, me auxiliou nos momentos mais difíceis e esteve celebrando comigo os momentos mais felizes também. Obrigada por sempre me apoiar, e por acreditar em mim quando nem eu acreditava. Todas as vezes que estive nervosa ou ansiosa, ele esteve junto a mim e isso me fez ter forças para continuar. Obrigada por todo o amor , por toda a paciência comigo, eu sempre digo que tu é o meu anjo.

Agradeço também aos meus sogros, que são pessoas incríveis e que sempre estiveram presentes durante esse período. Sempre me deram muito amparo e carinho nessa trajetória, eles se tornaram a minha segunda família e tornaram o caminho muito mais leve.

Agradeço aos meus tios e tias, por sempre me apoiarem e, principalmente a minha tia Nadir, que eu adotei na verdade como uma vó e que me faz acreditar que existe pessoas com uma bondade gigante, além de ver a vida com mais alegria e espontaneidade.

Agraceço a professora Fernanda Visioli que é uma inspiração de mulher para mim. Topou me auxiliar nessa caminhada que é a conclusão de curso e sempre foi muito atenciosa comigo e presente. Com ela adquiri um maior conhecimento, além de ter criado encanto pela área da patologia. Sou muito grata por ter escolhido ela como orientadora, não poderia ter sido melhor.

Agradeço a Camila Ferri, que por obra do destino foi minha fiscal do vestibular e desde lá se tornou uma pessoa muito especial na minha vida. Posso dizer que ela esteve presente no início, meio e fim da minha graduação. Foi ela que abriu caminhos

e me guiou até a Fernanda, além de ter sido essencial para minha aprendizagem na área científica.

Agradeço também a Natália e ao Douglas, que fizeram o trabalho juntamente comigo. Tive o grande prazer de conhecer mais eles no final da Graduação e sou grata por isso. Obrigada pela paciência e pela união, vocês foram imprescindíveis para elaboração desse trabalho.

Agradeço a banca avaliadora, professora Márcia e professora Lisiane por ter aceito fazer parte dessa finalização de ciclo, que é algo tão importante nas nossas vidas. Não tive tanto contato com vocês na vida acadêmica, mas sempre tive muita admiração por tudo que vocês representam. É um privilégio e alegria ter vocês nesse momento tão especial.

Agradeço as minhas amigas de Sapiranga, que antes mesmo de começar a Faculdade já faziam parte da minha vida. A nossa amizade fez esses anos se tornarem algo leve e cheio de alegrias, estar com vocês é tão bom. Meu coração se enche de carinho, e sou muito grata por todo o apoio e ombro amigo que vocês me proporcionaram. Todas palavras que vocês me disseram foram extremamente importantes para me fortificar.

Agradeço as minhas colegas e amigas, Liliana, Ana, Bárbara, Natália, Helena e Vanessa. Minha caminhada teve muito mais sentido quando eu conheci vocês. Vocês me ouviram, me apoiaram, me xingaram quando necessário, e me fizeram rir e ter tantos momentos felizes durante a graduação. Sem a companhia de vocês a caminhada teria sido maçante, vocês fizeram tudo mais leve e cheio de alegria. Obrigada por tudo amigas.

Agradeço, especialmente a minha amiga, colega e dupla Liliana. Sempre destaco que conheci a Liliana quando ainda fazia curso preparatório, mas nunca procurei ter contato com ela. Mas a vida traça tantas coisas boas para nós, e por obra dela, eu e a Liliana nos conhecemos no inicio da Faculdade e nossa energia foi muito compatível. Com ela eu compartilhei meus medos, ansiedades, e tive a oportunidade de a ter como dupla durante toda a faculdade. Com ela o período de graduação teve sentido e os momentos que compartilhamos foram incríveis, sou tão grata por ela ter entrado na minha vida.

Agradeço também a minha amiga e colega Bárbara, com ela vivi intensamente os últimos 2 anos da graduação. Com o apoio dela consegui superar muito dos meus

medos, e ansiedade. Deus me deu um presente enorme quando nos aproximou, ele nem faz ideia de como sou grata por isso. Obrigada por ser luz na minha vida e por ter sempre me acolhido, nunca medistes esforços para se fazer presente.

Agradeço a minha psicóloga, que me auxiliou a enfrentar todos os meus medos e angústias durante a pandemia juntamente com esse final de graduação.

Agradeço aos pacientes que atendi e a toda Faculdade de Odontologia. Todos tem uma parte importante na minha trajetória. Minha aprendizagem e crescimento profissional não teria sido o mesmo sem eles.

Agradeço aos professores, alguns foram mais presentes na minha vida e criei um laço maior. Mas todos foram essenciais, e cada um com seu jeito, agregou de alguma forma no meu crescimento profissional e pessoal durante esse período. Também agradeço a minha preceptora, que me ensinou muito durante o estágio I e II.

Por fim agradeço a todos os amigos que fiz durante a graduação e que de alguma forma me ajudaram, assim como meus colegas do ATO 2020/2, que presenciaram e passaram comigo todos esses momentos difíceis da nossa formação. Obrigada colegas, por terem tornado essa turma tão especial e unida durante esses 5 anos.

RESUMO

Biomarcadores para prognóstico do câncer são ferramentas extremamente importantes para melhorar a tomada de decisão personalizada e para prever a resposta ao tratamento. GRP78 é uma chaperona do retículo endoplasmático (ER) frequentemente superexpresso em células cancerosas e, em algumas situações, pode ser translocada para outros compartimentos celulares como a membrana plasmática (MP). Esta proteína está associada a vias de sinalização pró-sobrevivência em condições estressantes. Portanto, o objetivo desta revisão sistemática foi avaliar a expressão de GRP78 em diferentes tipos de câncer e se os seus níveis estão relacionados aos desfechos de sobrevida e prognóstico. Esta revisão foi conduzida de acordo com as diretrizes PRISMA e registrada no PROSPERO (CRD42021241801). Nos bancos de dados PubMed, Embase, Scopus, Lilacs foram pesquisados estudos com amostras de tecido de câncer humano, onde os níveis de imunohistoquímica de GRP78 foram correlacionados com parâmetros clínicos, histológicos e prognósticos. Um total de 91 manuscritos foi incluído, totalizando 11.199 amostras de tumor de pacientes. A maioria das amostras tumorais apresentou maior expressão de GRP78 em comparação ao tecido não tumoral correspondente. Na presente revisão, GRP78 foi encontrado no citoplasma em 48,3% dos estudos, 2,2% na MP, 9,8% tanto na MP quanto no citoplasma, no citoplasma e núcleo em 3,3%, enquanto em 30, 7% dos estudos o compartimento celular não foi informado. Em 67% dos estudos, GRP78 foi associado a um pior prognóstico em cânceres dos tipos oral, nasofaríngeo, esofágico, gástrico, pâncreas, fígado, melanoma, astrocítico, próstata, trato urinário, mama, ovário, endométrio, mesotelioma, pulmão, e mieloma. Já em 12% estava associado a menor agressividade, compreendendo: tumores de neuroblastoma, laríngeo, hipofaríngeo, carcinoma tímico avançado e linfoma não Hodgkin. Os 21% restantes dos estudos não detectaram associação significativa, entre eles os tumores colorretais e o carcinoma adenóide cístico. A correlação entre os níveis de GRP78 e a resposta ao tratamento foi dependente de drogas e do tipo de tumor. Em conclusão, GRP78 é um importante biomarcador prognóstico para diferentes tipos de câncer e, conseqüentemente, um alvo terapêutico promissor.

Palavras-chave: GRP78, Prognóstico; BIP; câncer; biomarcador; revisão sistemática.

ABSTRACT

Biomarkers for cancer prognostication are extremely important tools to improve personalized decision-making and to predict treatment response. GRP78 is an endoplasmic reticulum (ER) chaperone frequently overexpressed in cancer cells, and in some situations, it can be translocated to other cellular compartments as the plasma cell membrane (PCM). This protein is associated with pro-survival signaling pathways in stressful conditions. Therefore, the aim of this systematic review was to evaluate the expression of GRP78 in different types of cancer and whether it is related to survival and prognosis outcomes. This review was conducted according to PRISMA guidelines and registered at PROSPERO (CRD42021241801). PubMed, Embase, Scopus, Lilacs databases were searched for studies with human cancer tissue samples, where GRP78 immunohistochemical levels were correlated with clinical, histological, and prognostic parameters. A total of 91 manuscripts was included, totaling 11.199 patient's tumor samples. Most of the tumor samples showed higher expression of GRP78 in comparison to corresponding non-tumoral tissue. In the present review, GRP78 was found in the cytoplasm in 48,3% of studies, 2.2% in the PCM, 9,8% in both PCM and cytoplasm, in the cytoplasm and nucleus in 3,3%, while in 30,7% of the studies the cell compartment was not informed. In 67% of the studies, GRP78 was associated with a worse prognosis in melanoma, gastric, pancreas, esophageal, astrocytic, prostate, liver, breast, urinary tract, mesothelioma, lung, oral, nasopharyngeal, ovarian, endometrial, and myeloma cancers. Whereas in 12% it was associated with less aggressiveness, comprising: neuroblastoma, laryngeal, hypopharyngeal, advanced thymic carcinoma, and non-Hodgkin lymphoma tumors. The remaining 21% of the studies have not detected any significant association, among these, were colorectal and adenoid cystic carcinoma tumors. The correlation among GRP78 levels and treatment response was drug-dependent and tumor-dependent. In conclusion, GRP78 is an important prognostic biomarker for different types of cancer and consequently, a promising therapeutic target.

Keywords: GRP78; ; prognosis; BIP; cancer; biomarker; systematic review.

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1 INTRODUÇÃO

1.1 Carcinogênese

O crescimento desordenado de células com potencial de invadir tecidos e órgãos, caracteriza o grupo de doenças ditas como câncer (INCA, 2019). A divisão dessas células pode ser altamente agressiva e incontrolável, tendo a capacidade de invadir tecidos e órgãos vizinhos ou distantes, ocasionando o processo chamado de metástase (INCA, 2019).

As neoplasias, benignas ou malignas, são doenças genéticas, as quais são originadas de mutações que podem ser transmitidas hereditariamente pela linhagem germinativa, ou adquiridas no próprio tecido (FUKUDA; OHMORI; SAKASHIT, 2012; LICHTENSTEIN, 2009). A carcinogênese é o processo de desenvolvimento de uma neoplasia maligna, sendo determinada pelos efeitos cumulativos referentes à exposição de diferentes agentes carcinógenos, a partir de uma frequência e por um período de tempo, além da relação entre eles (FUKUDA; OHMORI; SAKASHIT, 2012).

O processo da carcinogênese é composto por três estágios: iniciação, promoção e progressão. Na fase de iniciação, não há detecção clínica de um tumor e as células tornam-se geneticamente alteradas devido a ação dos agentes carcinogênicos. Na promoção, os oncogenes estimulam a proliferação das células iniciadas propiciando o acúmulo de mais mutações, levando a terceira fase em que ocorre o estabelecimento do fenótipo celular maligno, e a multiplicação descontrolada e irreversível das células ocasionará a manifestação clínica da doença (INCA, 2019).

As mutações que se acumulam nas neoplasias malignas permitem que as mesmas adquiram capacidades que permitem a proliferação celular, invasão tecidual e o desenvolvimento de metástases. Além do mais, alterações em processos fundamentais como a resistência à morte celular, e a evasão de inibidores de crescimento, permitem a imortalidade replicativa e também induzem ao processo de angiogênese (HANAHAN; WEINBERG, 2011; HSU et al., 2020). Durante a carcinogênese a célula acumula alterações suficientes que a fazem perder a capacidade de reparo de DNA e indução à apoptose associado a uma proliferação intensa e descontrolada (HANAHAN; WEINBERG, 2011).

A desregulação da apoptose é um dos eventos mais comuns para o desenvolvimento do câncer, e seu controle envolve genes supressores de tumores, oncogenes, genes da família Bcl-2, receptores de fatores apoptóticos, genes mitocondriais e caspases (JAIN et al., 2014).

Durante a carcinogênese a proliferação celular excessiva, gradualmente, causa alterações metabólicas no microambiente. Devido à população crescente de células o microambiente de tumores sólidos difere do microambiente dos tecidos normais, sendo caracterizado pela privação de nutrientes, hipóxia, baixo pH, e pelo desequilíbrio entre produção e remoção de espécies reativas de oxigênio chamada de estresse oxidativo (HAZARI et al., 2016).

O crescente estresse, causado pela massa celular em intensa proliferação associado a deficiência nutricional neste microambiente, pode desencadear um processo catabólico onde as células degradam componentes próprios a fim de produzir energia e reciclar suas organelas mantendo a sobrevivência e a homeostase celular, chamado de autofagia (MATHEW; WHITE, 2011).

Além do mais, no microambiente tumoral, muitos fatores externos e internos perturbam a síntese e maturação proteica resultando no acúmulo de proteínas mal dobradas no lúmen do retículo endoplasmático (RE), causando o estresse no RE (PAPAIOANNOU; CHEVET, 2017). Quando isso acontece é acionado um mecanismo adaptativo chamado Resposta da proteína mal dobrada, ou *Unfolded Protein Response (UPR)* para ajudar a célula a lidar com o estresse e restaurar a homeostase da proteína no RE (PAPAIOANNOU; CHEVET, 2017). Uma das respostas desencadeadas pela UPR é a indução do processo autofágico para ajudar a eliminar as proteínas alteradas acumuladas no interior do RE (GIAMPIETRI et al., 2015; HAZARI et al., 2016; PIHÁN; HETZ, 2020).

1.2 Estressse no Reticulo Endoplasmatico e ativação da UPR

O retículo endoplasmático (RE) é um compartimento citoplasmático onde proteínas e lipídios são sintetizados (LEE, 2005). Nesse mesmo local estão presentes as chaperonas, que facilitam o dobramento adequado dos polipeptídeos, os quais estão sofrendo constantemente o risco de dobramento incorreto, sendo a proteína

regulada por glicose 78 (GRP78) uma das principais representantes do grupo das chaperonas presentes no RE. As chaperonas emitem um sinal de retenção no RE, permitindo que as proteínas sejam mantidas no RE num estado favorável ao enovelamento (LEE, 2005; WANG et al., 2017b). No câncer, o acúmulo de proteínas mal dobradas pode ser resultado de mutações genéticas e rearranjos genômicos, e também consequência do estresse causado pelo microambiente tumoral nas células (BAILLY; WARING, 2019).

A massa sólida do tumor, propicia um ambiente com condições insuficientes de oxigênio em seu interior. Devido a baixa concentração de vasos sanguíneos e a hipóxia gerada no microambiente tumoral é induzida a autofagia por meio de uma família de proteínas HIF (fator induzido por hipóxia). A proteína HIF-a é ativada e os dominios atípicos da proteína BH3 interrompem o complexo BCL-2-Beclin-1, propiciando a autofagia, sem induzir morte celular (KOCATURK et al., 2019).

Além da hipóxia, o microambiente fica caracterizado pela pouca disponibilidade de glicose e outros nutrientes, assim como baixo pH. A glicosilação de proteínas e produção de ATP é afetada pela baixa concentração de glicose (NAGELKERKE et al., 2014).

Dessa forma, o estresse do microambiente tumoral também é capaz de gerar o acúmulo de proteínas mal dobradas no lúmen do retículo endoplasmático (RE). O retículo endoplasmático é responsável pela maturação e pelo enovelamento tridimensional de proteínas antes de serem transportadas para o meio intracelular ou extracelular Esse processo é mediado com auxílio de proteínas chaperonas e é dependendente de energia, da homeostase de íons cálcio e homeostase redox (WANG; KAUFMAN, 2014).

Vários fatores presentes no microambiente tumoral podem afetar a função do RE, tais como: hipóxia, depleção de energia e estresse oxidativo, resultando em concentração elevada de proteínas imaturas, favorecendo o estresse do RE. O grande acúmulo intracelular de agregados proteicos é tóxico e pode ter como resultado a morte celular. Por esse motivo, as células desenvolveram uma resposta adaptativa como resposta ao estresse. A UPR é uma via de transdução de sinal, a qual possibilita a comunicação entre o RE e o núcleo, o que ativa a expressão de diversos genes-alvos responsáveis pela homeostase proteica e celular, através dos processos de

translocação, glicosilação, degradação e transporte proteico (RON; WALTER, 2007; SCHRÖDER; KAUFMAN, 2005).

A ativação da UPR visa a promoção da homeostase diminuindo a quantidade de proteínas nascentes bloqueando a tradução proteica transitoriamente e inicialmente, aumentado a capacidade de dobramento através da ativação das chaperonas e aumentando a capacidade de degradação das proteínas mal dobradas pelo proteassoma ou pela autofagia. Em casos de estresse exacerbado no RE, em que não foi possível a correção dos danos, a UPR pode ativar a apoptose da célula (NAGELKERKE et al., 2014).

A via UPR é ativada, na tentativa de restabelecer a homeostase, sendo regulada por três proteínas transmembranas, que são elas: IRE1α (enzima dependente de inositol-1), ATF6 (fator de ativação transcricional 6) e PERK (quinase do retículo endoplasmático PKR-like)**.** Normalmente essas proteínas transmembranas se encontram ligadas à chaperona GRP78, pelo domínio amino-terminal da PERK e da IRE1, e ao domínio carboxi-terminal da proteína ATF6, quando o RE se encontra em homeostasia. Entretanto, quando há situações de estresse as três proteínas são liberadas através do desligamento da GRP78 que é recrutada para auxiliar no enovelamento proteico, como está ilustrado na figura 1 (GIAMPIETRI et al., 2015), dessa forma, a GRP78 sinaliza o estresse no RE e a ativação da UPR (NAGELKERKE et al., 2014).

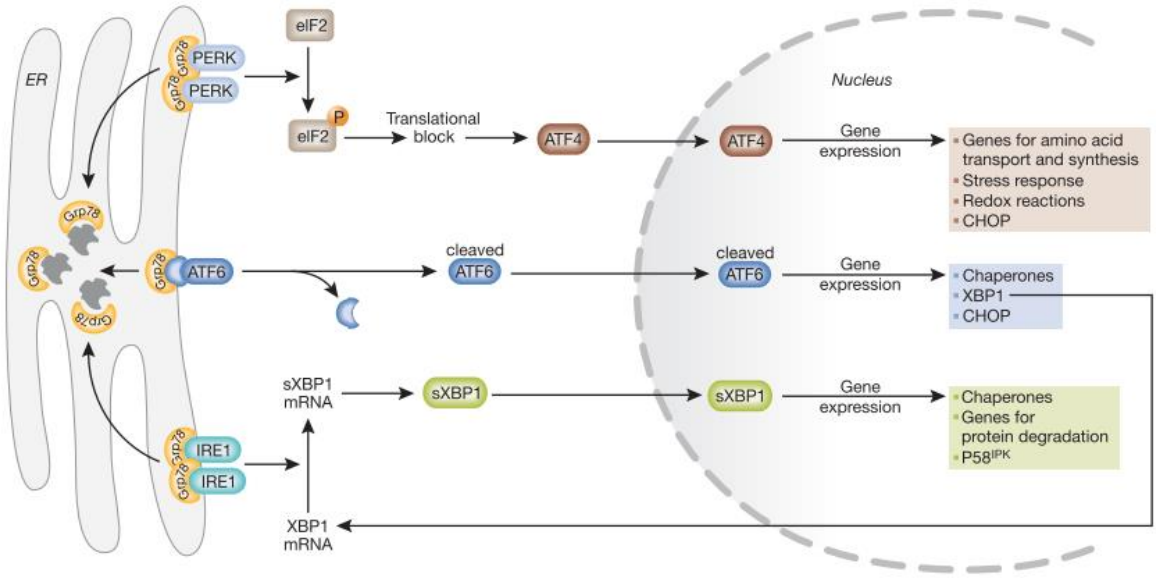

Figura 1. Esquema da via UPR (Fonte:SZEGEZDI et al., 2006)

Para possibilitar regulação da homeostase, devido ao estresse de diferentes insultos fisiológicos ou patológicos, as células usam diversos recursos. No primeiro momento, ocorre o bloqueio da tradução de proteínas formadas no RE para diminuir a chegada de proteínas nascentes. Como segunda tentativa de homeostase, ocorre a indução e aumento de chaperonas no RE. Em terceiro, o RE se expande para tentar suportar a alta carga de proteínas e em seguida, começa a degradação de proteínas que não estão dobradas corretamente (ERAD- Degradação de proteínas associadas ao RE), a qual consiste em 2 mecanismos: ERAD tipo I que causa degradação de agregados proteicos dependente de proteassoma e visa apenas proteínas solúveis mal dobradas e o mecanismo ERAD tipo II dependente de lisossoma, sendo uma via autofágica tanto para proteínas solúveis quanto insolúveis (RASHID et al., 2015).

A sinalização para ativação da UPR se dá por três cascatas coordenadas por três fatores de transcrição: ATF4 (para PERK), ATF6 clivado (para ATF6) e sXbp1 (Para IRE1), como ilustrado na figura 2 (ZHANG; QU; JIANG, 2017). A via de sinalização PERK-eIF2 a-ATF4-CHOP está associada ao bloqueio da tradução das proteínas no lúmen do ER e na redução da concentração de proteínas nascentes no local. Além disso, CHOP é um fator de transcrição responsável pela regulação da

autofagia e apoptose, através da inibição de Mtorc1. Outra via é a IRE-1, que desempenha papel por meio de sinalização de JNK1 e pela função de endonuclease, com remoção de itron na transcrição que codifica o fator de transcrição XBP1. Em seguida ocorre ativação de proteínas autofágicas, como LC3B e Beclin1 (ZHANG; QU; JIANG, 2017).

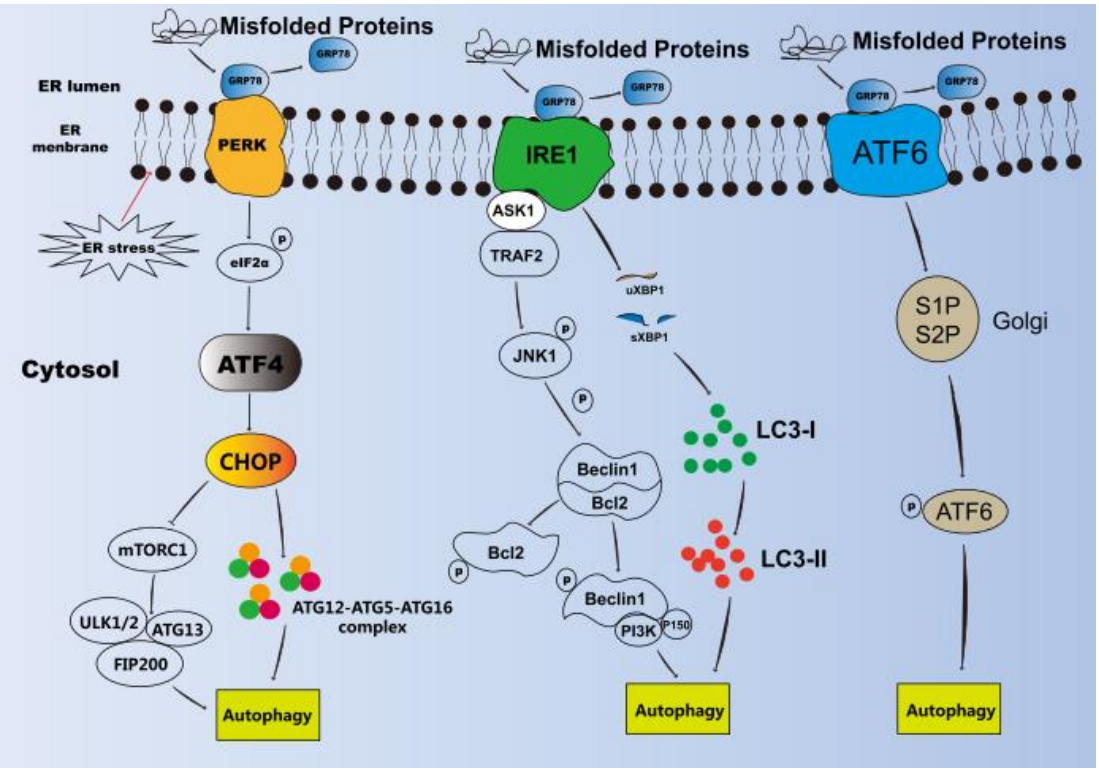

Figura 2. Cascatas de sinalização da UPR (Fonte: ZHANG; QU; JIANG, 2017)

A via de ATF6, que é um fator de transcrição liberado da membrana por clivagem proteolítica, pode induzir autofagia através da influência que exerce no núcleo e no complexo de Golgi. Com ajuda das proteases S1P E S2P, o ATF6 ativado pode regular reversamente algumas chaperonas, como é o caso do GRP78 E GRP94. ATF6 também pode estimular XBP1 para auxiliar nos processos de dobramento, secreção e degradação das proteínas no RE (ZHANG; QU; JIANG, 2017).

1.3 GRP78

A proteína regulada por glicose 78 (GRP78) ou proteína de ligação de imunoglobulina (BIP) é uma chaperona e faz parte da família de proteínas HSP70 (Heat Shock Protein 70). Essa proteína é encontrada, principalmente, no RE da célula, mas em algumas situações também poderá ser encontrada na mitocôndria e no núcleo celular. O GRP78 também pode ser encontrado ligado à membrana celular e na forma circulante, quando se desprende da membrana e é secretado para fora da célula (BAILLY; WARING, 2019). No RE, GRP78 atua para promover a homeostasia do local, e auxilia no dobramento de proteínas que não estão dobradas corretamente (resposta UPR) (LU; LUO; ZHU, 2020) porém caso não seja possível atingir a configuração correta da proteína, ela é degradada pelo sistema ERAD, (IBRAHIM; ABDELMALEK; ELFIKY, 2019) e se ainda não ocorrer o equilíbrio celular, se o estresse for intenso ou persistente, a célula entra em apoptose através da ativação de vias pró-apoptóticas: caspase 12, JNK e CHOP como mostra a figura 3 (ELFIKY et al., 2020; LU; LUO; ZHU, 2020).

GRP78 é composto por dois domínios de ligação, o domínio de ligação ao nucleotídeo (NBD) e outro de ligação ao substrato (SBD). O SBD é responsável pela interação aos polipeptídeos mal dobrados, enquanto o NDB é encarregado de capturar e promover a hidrólise do ATP, fornecendo energia necessária para prevenir agregação da proteína (BAILLY; WARING, 2019).

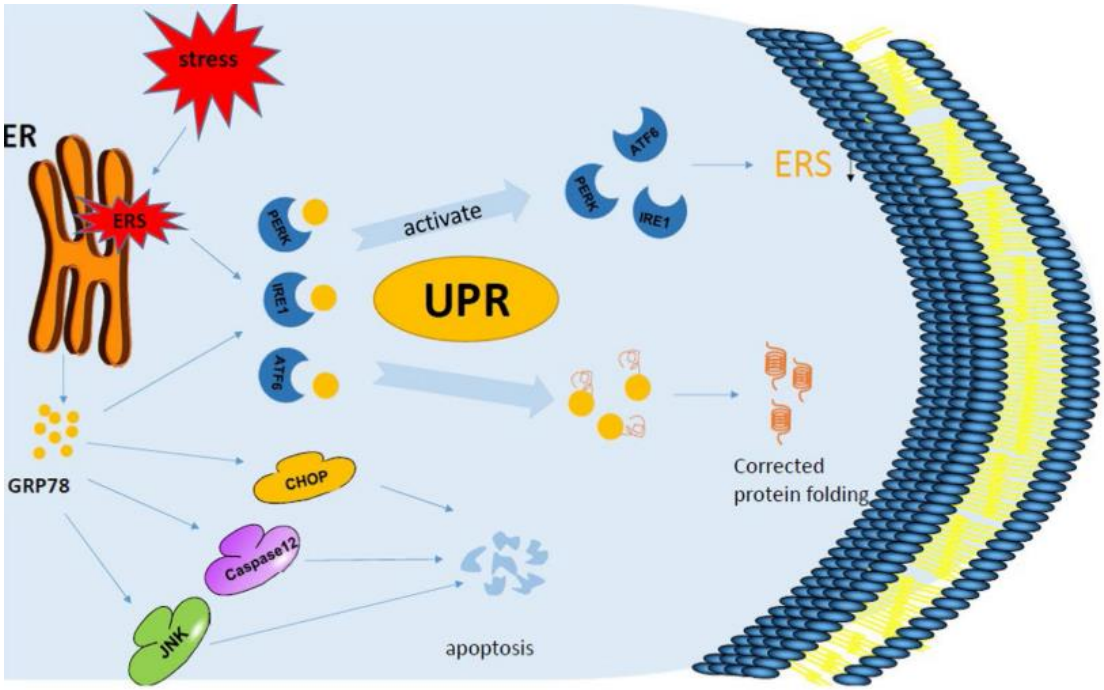

Figura 3. Funções de GRP78 no RE Fonte: (LU; LUO; ZHU, 2020).

Em situações de homeostase celular, GRP78 encontra-se ligado de forma inativa aos três sensores da UPR. Para ativação da UPR em momentos de estresse, ocorre a separação do GRP78 dessas proteínas. Em situações em que há o estresse do RE, como no câncer, observa-se um aumento dos níveis da proteína GRP78 (IBRAHIM; ABDELMALEK; ELFIKY, 2019). A expressão aumentada de GRP78 é observada em células tumorais, em diversos tipos de câncer, como mama, pulmão, estômago, entre outros, que já revelaram possuir níveis elevados de sua expressão, correlacionando-o positivamente com a proliferação e agressividade tumoral (BAILLY; WARING, 2019)**.** O aumento da expressão desta chaperona e sua relação com maior agressividade tumoral pode estar diretamente conectado ao fato da molécula ligar-se a caspases, responsáveis pela apoptose celular e, dessa forma, inibir sua ativação, tornando as células mais resistentes aos danos sofridos no DNA (IBRAHIM; ABDELMALEK; ELFIKY, 2019; LUO; LEE, 2013; VISIOLI et al., 2014).

1.4 GRP78 na superfície celular

GRP78 pode ser deslocar do RE para a membrana plasmática da célula, sendo denominado *CELL-SURFACE* (CS-GRP78). O tetra-peptídeo C terminal (KDEL) é o receptor responsável pela retenção do Grp78 dentro do lúmen do ER. No entanto,

condições de estresse celular ou patológicas são capazes de gerar aumento da expressão intracelular de GRP78, promovendo a saturação dos receptores KDEL, tendo como consequência a evasão desta chaperona para a membrana plasmática. GRP78 pode ser translocado e ancorado à superfície celular por ligação à ER-cochaperona HTJ-1 / MTJ-1 sendo promovida pelo excesso do fosfolipídeo1-palmitoil-2-araquidonoil-sn-glicero-3-fosfocolina (OxPAPC), o qual tem interação direta com GRP78(IBRAHIM; ABDELMALEK; ELFIKY, 2019). A presença de CS-GRP78 foi associada à agressividade de alguns tumores, como câncer de mama, ovário, pâncreas e cólon. Além disso, CS-GRP78 pode funcionar como um co-receptor e possibilitar a entrada de diversos patógenos, facilitando o desenvolvimento de várias doenças como: Papiloma Vírus (HPV); Zika Virus (ZIKV); vírus da dengue (DENV); Vírus Ebola (EBOV); Hepatite C (HCV) e outros (ELFIKY et al., 2020).

GRP78 não possui domínio transmembrana, mas atua como receptor e co-receptor para ligantes solúveis e através da interação com diversas proteínas encontradas na membrana, é mencionado como um possível transdutor do sinal de células tumorais (CASAS, 2017). Ele possui papel crucial na sinalização celular, inflamação, proliferação, invasão apoptose e imunidade. A ligação de CS-GRP78 com α2-macroglobulina promove proliferação do tumor através de uma cascata de sinalização (ativação de ERK1/2, p38 MAPK) e sobrevivência celular pela ativação de AKT e NF-KB. Além disso, o crescimento exacerbado do tumor pode estar relacionado à ligação de GRP78 à proteína CRIPTO, pois esta ligação está associada à inibição da sinalização de TGF-B (fator de crescimento transformador B). (NI; ZHANG; LEE, 2011). Também é descrito que a presença de GRP78 na superfície de células endoteliais auxilia no processo de angiogênese (formação de novos vasos sanguíneos), facilitando, assim, a progressão tumoral (NI; ZHANG; LEE, 2011).

Quando ligado à superfície celular, além do papel citoprotetor de GRP78, esta atua também na remodelação do citoesqueleto, na adesão célula-matriz pela interação com integrina-α e regulação de quinase de adesão focal (FAK), processos relacionados à migração e invasão tumoral (CASAS, 2017). Quando secretada, GRP78 pode ser encontrada na circulação periférica, influenciando a sinalização celular e associada a propriedades imunomodulatórias e anti-inflamatórias (CASAS, 2017; LU; LUO; ZHU, 2020).

1.5 GRP78 e a resistência ao tratamento anti-tumoral

A célula tumoral pode desenvolver resistência às drogas que são usadas no tratamento antitumoral. Grande expressão dos níveis de GRP78 em células cancerosas podem ser um indicativo de maior resistência do tumor ao tratamento. Com isso, GRP78 se torna um importante alvo para aprimoramento da terapia tumoral. (LU; LUO; ZHU, 2020). Acredita-se que são dois mecanismos responsáveis pela resistência ao tratamento quimioterápico induzida por GRP78, sendo elas a ativação mediada por receptor da via AKT/PI3K e a indução da via UPR. Em ambas situações, GRP78 atua como um fator anti-apoptótico tornando a célula tumoral mais resistente à morte celular e, consequentemente, mais resistente às diferentes modalidades terapêuticas (ELFIKY et al., 2020).

Algumas drogas podem ser usadas para atingir GRP78 e suas proteínas-alvo, inibindo a progressão de células tumorais e impedindo a replicação de patógenos como vírus e bactérias. Algumas substâncias podem ligar-se ao GRP78 no RE, regulando de forma negativa sua expressão e a partir disso induzir um aumento do estresse local, ocasionando a autofagia, morte celular e outros efeitos antitumorais (LU; LUO; ZHU, 2020).

Estratégias que buscaram inibir ou inativar GRP78 observaram aumento da apoptose, redução da proliferação celular e regulação negativa da via PI3K/Akt/Mtor, que tem papel importante no ciclo celular, crescimento e sobrevivência tumoral. Sendo assim, os tratamentos antitumorais podem se beneficiar da redução da superexpressão de GRP78, reduzindo assim a resistência do tumor à radioterapia e à quimioterapia (ELFIKY et al., 2020)**.**

1.6 Biomarcador

Biomarcadores são moléculas biológicas que nos ajudam a identificar processos de normalidade e anormalidade que ocorrem no corpo humano , os quais clalssificam-se em preditivos, diagnósticos e prognósticos. Pode-se destacar como biomarcadores, o uso de proteínas, exemplo GRP78 , além do uso de ácidos nucleicos e outros, que podem ser encontrados na circulação, secreções ou de forma mais invasiva, quando se faz necessário a biópsia de um tecido em específico.O uso

de biomarcadores pode nos trazer informações relevantes no percurso de uma doença, como em sua detecção, na na sua recorrência ou para que se consiga prever determinada resposta ao tratamento e assim determinar o mais eficaz. Para que um biomarcador seja classificado como bom e tenha utilidade clínica, é necessário que haja grande quantidade de estudos que validem seu uso. (HENRY; HAYES, 2012).

Desfechos clínicos como sobrevida global e sobrevida livre de doença podem ser vistos através do uso de biomarcadores classificados como prognóstico. (RIVERA et al., 2017). Sendo assim, podem sugerir a possibilidade da doença estudada acontecer, da provável recorrência e progressão. No câncer oral ainda não se está estabelecido um bom biomarcador de prognóstico, no entanto alguns tipos de cânceres já revelam possuí-lo, de forma a auxiliar na melhor escolha do tratamento da doença, aumentando os níveis de sucesso e diminuindo a taxa de mortalidade do câncer. (RIVERA et al., 2017)

2 OBJETIVOS

2.1 Objetivo geral

Desenvolver uma revisão sistemática da literatura sobre a relação entre os níveis proteicos de GRP78 em amostras tumorais de diferentes tipos de câncer e o comportamento e prognóstico tumoral.

2.2 Objetivos específicos

Determinar se há aumento dos níveis de GRP78 em cânceres quando comparados a tecidos normais ou benignos.

Determinar se há associação entre os níveis de GRP78 e características clínico-patológicas dos tumores avaliados.

Determinar se há relação entre os níveis de GRP78 e a resposta ao tratamento dos tumores avaliados.

Determinar se há relação entre os níveis de GRP78 e desfechos de sobrevida dos pacientes acometidos pelos tumores estudados.

3 ARTIGO CIENTÍFICO

Periódico: Critical Reviews in Oncology/Hematology

IS GRP78 (GLUCOSE-REGULATED PROTEIN 78) A PROGNOSTIC BIOMARKER IN DIFFERENTS TYPES OF CANCER? A SYSTEMATIC REVIEW

GRP78 é um bom biomarcador de prognóstico tumoral? Uma revisão sistemática

ABSTRACT

Biomarkers for cancer prognostication are extremely important tools to improve personalized decision-making. GRP78 is a chaperone frequently overexpressed in cancer. Therefore, the aim of this systematic review was to evaluate the expression of GRP78 in different types of cancer and whether it is related to prognosis outcomes. This review was conducted according to PRISMA guidelines and registered at PROSPERO. Databases were searched for studies with human cancer samples, where GRP78 immunohistochemical levels were correlated with clinical, histological, and prognostic parameters. 91 manuscripts were included, totalizing 11.199 patient's tumor samples. In 67% of the studies, GRP78 was associated with a worse prognosis in melanoma, gastric, pancreas, esophageal, astrocytic, prostate, liver, breast, urinary tract, mesothelioma, lung, oral, nasopharyngeal, ovarian, endometrial, and myeloma cancers. Whereas in 12% it was associated with less aggressiveness, comprising: neuroblastoma, laryngeal, hypopharyngeal, advanced thymic carcinoma, and non-hodgkin lymphoma tumors. In conclusion, GRP78 is an important prognostic biomarker.

Keywords: GRP78; cancer ; prognosis ; biomarker ; sistematic review.

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INTRODUCTION

Cancer is a multifactorial disorder and biologically characterized as an uncontrolled growth of cells with the ability to invade tissues and spread to neighboring or distant organs (HANAHAN; WEINBERG, 2011). Benign and malignant neoplasms are caused by genetic mutations and epigenetic alterations, transmitted in a hereditary way or acquired due to exposure to different carcinogenic agents throughout life (FUKUDA; OHMORI; SAKASHIT, 2012).

In 2020, there were 19,3 million new cases of cancer and 10,0 million deaths caused by these diseases worldwide. The cancer mortality rate is high; and it is considered the main cause of death of individuals under the age of 70 (SUNG et al., 2021). Thus, it is important to highlight that the main measures to decrease this rate are early diagnosis and prevention of this disease through the control of risk factors (CHAKRABORTY; NATARAJAN; MUKHERJEE, 2019).

Carcinogenesis is the process of cancer formation, consisting of 3 stages: initiation, promotion and progression (OLIVEIRA et al., 2007). The uncontrolled increase in cell proliferation is associated with inhibition of apoptosis and DNA repair. The multiplication of these cells causes metabolic changes in the microenvironment, promoted by nutritional scarcity, hypoxia, low pH, and oxidative stress (HAZARI et al., 2016).

In the tumor microenvironment, alterations in protein synthesis and maturation occurs, which corroborates the accumulation of misfolded proteins in the endoplasmic reticulum (ER), and results in stress in this compartment. Within the ER protein synthesis and maturation occurs with the aid of chaperones, responsible for folding the polypeptides that are constantly folded incorrectly. One of the main chaperones found in this compartment is the glucose-regulated protein 78 (GRP78), also known as BIP (Binding protein) and HSP5A (Heat-shock protein 5A) (LEE, 2005; WANG et al., 2017b).

In response to cellular stress, an adaptive mechanism called Unfolded Protein Response (UPR) is activated, which aims to restore cellular homeostasis. Initially, the UPR promotes a decrease in the amount of nascent proteins and blocks protein translation (PAPAIOANNOU; CHEVET, 2017). There is also an increase in protein

folding through the activation of chaperones and an increase in the degradation of proteins poorly folded by the proteasome or autophagy. Cell apoptosis occurs if damage is not repaired (NAGELKERKE et al., 2014).

The GRP78 expression and protein levels are increased in several types of cancer, being previously related to the proliferation and aggressiveness of the tumor (BAILLY; WARING, 2019). This may occur because GRP78 is able to bind to caspases, inhibiting the activation of apoptosis, which makes cells more resistant to DNA damage (IBRAHIM; ABDELMALEK; ELFIKY, 2019; LUO; LEE, 2013; VISIOLI et al., 2014). GRP78 is found, mainly in the ER, but it can be found in other compartments such as the mitochondria and nucleus. It can also be found attached to the cell membrane or in the peripheral circulation, when secreted (BAILLY; WARING, 2019). GRP78 can be moved from the ER to the plasma membrane of the cell, being (ELFIKY et al., 2020). The presence of CS-GRP78 has been associated with the aggressiveness of some tumors, such as breast, ovarian, pancreatic and colon cancer. In addition CS-GRP78 can function as a coreceptor and allow the entry of several pathogens (ELFIKY et al., 2020). GRP78 does not have a transmembrane domain, but it acts as a receptor and co-receptor for soluble ligands and through the interaction with several proteins found in the membrane, it is mentioned as a possible tumor cell signal transducer (CASAS, 2017). CS-GRP78 seems to play an important role in cell signaling, inflammation, proliferation, invasion, apoptosis and immunity (IBRAHIM; ABDELMALEK; ELFIKY, 2019).

The overexpression of GRP78 in cancer cells indicates that this chaperone may be an excellent prognostic biomarker in different types of cancer. A prognostic biomarker suggests the likelihood of disease, recurrence or progression; which may be important in defining treatment (RIVERA et al., 2017). If GRP78 is a good biomarker of tumor aggressiveness, it can also improve treatment decisions. Therefore, the present study aims to develop a systematic review of the literature to analyze the relationship between protein levels of GRP78 in tumor samples of different types of cancer, their behavior and tumor prognosis.

MATERIALS AND METHODS

Search strategy

This study was conducted according to the PRISMA checklist. The protocol for this systematic review was registered at PROSPERO (International Prospective Register of Systematic Review) under the protocol number CRD42021241801.

A systematic search was carried out in the following databases: PUBMED, EMBASE, SCOPUS, and LILACS. The complete Search strategy for Pubmed is:

((molecular chaperone GRP78[Supplementary Concept] OR molecular chaperone GRP78[tw] OR immunoglobulin heavy chain-binding protein[tw] OR glucose regulated protein 78 kDa[tw] OR heat-shock protein 5[tw] OR molecular chaperone BiP[tw] OR BiP molecular chaperone[tw] OR Ig heavy chain binding protein[tw] OR Grp78[tw] OR GRP-78[tw] OR glucose regulated protein 78[tw] OR 78 KDa Glucose-Regulated Protein[tw] OR BIP[tw] OR binding immunoglobulin protein[tw] OR Immunoglobulin Heavy Chain-Binding Protein[tw] OR Binding-Immunoglobulin Protein[tw] OR HSPA5[tw] OR Heat Shock Protein Family A Hsp70 Member 5[tw] OR heat shock 70 kDa protein 5[tw] OR Heat Shock Protein 70 Family Protein 5[tw] OR Heat Shock Protein Family A Member 5[tw] OR HSP70 Family Protein 5[tw] OR MIF2[tw]) AND (neoplasms[mh] OR Neoplasm*[tw] OR Neoplasia*[tw] OR Tumor*[tw] OR Cancer*[tw] OR Malignanc*[tw] OR Malignant Neoplasm*[tw] OR Benign Neoplasm*[tw])) AND (prognosis[mh] OR Prognos*[tw] OR Prognostic Factor*[tw] OR survival[mh] OR survival[tw] OR survival rate[tw] OR overall survival[tw] OR disease-free survival[mh] OR Disease Free Survival[tw] OR observed surival rate[tw] OR death rate[tw] OR net survival rate[tw] OR cause-specific survival[tw] OR disease-specific survival[tw] OR relative survival[tw] OR median survival[tw] OR progression-free survival[mh] OR Progression Free Survival[tw] OR Event Free Survival[tw] OR metastasis-free survival[tw] OR distant metastasis–free survival[tw] OR Mortality[mh] OR Mortalit*[tw] OR Case Fatality Rate*[tw] OR Excess Mortalit*[tw] OR Mortality Decline*[tw] OR Mortality Determinant*[tw] OR Differential Mortalit*[tw] OR Age-Specific Death Rate*[tw] OR Mortality Rate*[tw])

The search was conducted on August 12, 2020 and comprised all articles published on this subject up to this date. Reference lists of included studies were manually searched to detect other potential studies.

Data collection and analysis

In the first stage of selection, the articles were evaluated based on the title and abstract, independently, by two reviewers, in case of disagreement a third evaluator decided whether or not to include the study. In this first stage, the eligibility for the systematic review will be assessed based on the “PICO” strategy: to identify studies reporting the role of GRP78 in tumor prognosis. In the second stage, the inclusion and exclusion criteria were applied to the full-length articles, as described below.

In the second selection stage, the full-texts of these studies were retrieved, thoroughly evaluated and decisions on inclusion / exclusion made. Any disagreements between them regarding the eligibility of specific studies was resolved through discussion with a third reviewer.

Exclusion and inclusion criteria

Inclusion criteria were prospective or retrospective studies assessing GRP78 levels by immunohistochemistry in cancerous human tissues. The exclusion criteria were studies not directly related to the theme of this review, duplicates, case reports, *in vitro*, animal models studies, and articles published in languages other than English.

After searching the databases, a total of 1865 references were retrieved, and 358 duplicate references were discarded. The 1507 remaining articles were assessed by title and abstract and 1341 references were excluded. Full-text analysis was performed for 166 articles,1 was excluded because it was not related to the theme, 4 were published in another language, 5 were abstracts, 33 have not performed GRP78 immunohistochemistry, 3 performed only animal analysis, 24 did not investigate any parameters and 5 had insufficient data. Finally, 91 articles were selected for the final review.

Data extraction

After the selection process, studies were submitted to evaluation and data extraction. For each study, qualitative and quantitative data were extracted as: type of study, first author, year of publication, country of origin, type of cancer, origin of the controls samples, number of cases and number of controls, immunohistochemistry methods, antibody used, protein quantification methodology, clinical parameters assessed, histological parameters assessed, prognostic parameters assessed, and main findings. When necessary, authors were contacted to provide further information.

All the selection and data extraction procedures were performed by 2 reviewers independently. Disagreements were discussed and decided by a third reviewer.

Outcome assessment

The main outcome prognostic outcomes assessed were overall survival, disease-free survival, death rate, and recurrence. Secondary outcomes also investigated were related to clinical parameters as: stage, location, size, locoregional or distant metastasis, metastasis-free survival, depth of invasion; and histological parameters as: differentiation grade and perineural invasion. Subgroup's analysis was performed considering: a) type of cancer b) histological subtype.

A descriptive synthesis of the findings from the included studies was performed, reporting if a significant association among GRP78 levels and the investigated parameters was detected.

RESULTS

The systematic search retrieved 91 studies regarding GRP78 expression in cancer samples (Figure 1). To facilitate data analysis, the results were separated according to the cancer site.

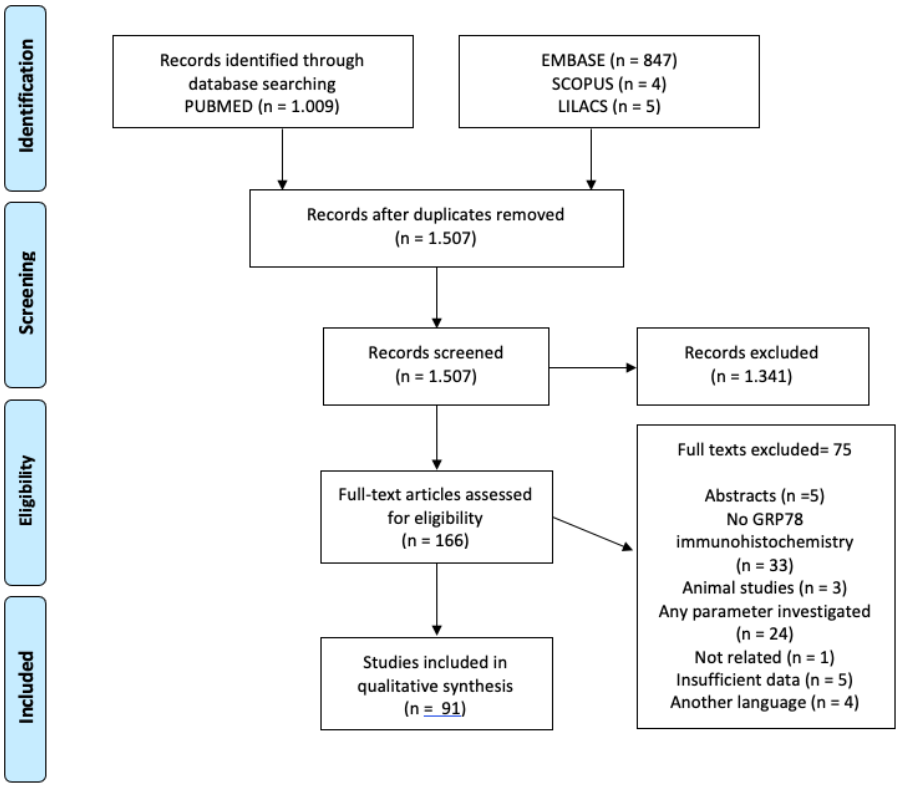

Figure 1. Flow Diagram of electronic search and studies selection.

HEAD AND NECK

Head and neck cancer includes tumors that affect the nasal cavity, sinuses, mouth, larynx and pharynx. Among the main risk factors are smoking, alcohol and HPV infection. In total, 10 articles were retrieved, with a sample of 860 (387 oral cancer, 241 nasopharyngeal cancer, 59 laryngeal cancer, 68 hypopharyngeal cancer, 105 adenoid cancer) individuals.

ORAL

Oral cancer affects lips, structures of the mouth, such as gums, cheeks, palate, tongue and the region under the tongue. Most cases are diagnosed in advanced

stages, both incidence and mortality have higher rates in men (SUNG et al., 2021). In total four articles were analyzed, including 387 patients. GRP78 was highly expressed in tumor samples rather than normal mucosa (HUANG et al., 2010; XIA et al., 2014). or precancerous lesions (LIN et al., 2010) In addition, GRP78 was higher in metastatic tumors, in comparison to primary tumors (KAIRA et al., 2016).

The results regarding the survival rate showed that the worst outcomes were associated with greater expression of GRP78, which was an independent prognostic factor (KAIRA et al., 2016; XIA et al., 2014). Most studies detected an association among higher levels of GRP78 and more aggressive oral tumors (KAIRA et al., 2016; LIN et al., 2010; XIA et al., 2014). However, Huang et al. (2010), found the opposite, GRP78 was weakly expressed in OSCC samples from patients with advanced stage tumors and neck lymph node metastasis in their sample.

GRP78 was positively associated with vascular and lymphatic invasion (KAIRA et al., 2016), as well as lymph node and distant metastasis (XIA et al., 2014). However, Huang et al (2010) detected the opposite, decreased GRP78 protein expression was significantly correlated with advanced tumor stage and neck lymph node metastasis. In addition, GRP78 levels were correlated with tumor grade, pathologic differentiation and tumor size (XIA et al., 2014) in one study, whereas Kaira et al. (2016) did not detect statistical significant differences.

NASOPHARYNGEAL

Most nasopharyngeal cancers are nasopharyngeal carcinoma (NPC), which is the most common type in the nasopharynx. This type of cancer, like many addressed here, has higher incidence and mortality rates in men (SUNG et al., 2021). Here two articles have been retrieved, including 241 patients. GRP78 expression was higher in tissue samples from NPC than in tissue samples from chronic rhinitis (FENG et al., 2018) and normal nasopharyngeal mucosa (YI et al., 2016). In addition, when the NPC was subdivided, the radio-resistant NPC showed greater expression of GRP78 compared to the radiosensitive NPC (FENG et al., 2018; YI et al., 2016). Besides that, higher GRP78 levels were correlated with positive lymph node metastasis (YI et al., 2016) and higher TNM stage (YI et al., 2016) .

LARYNGEAL

The manifestation of the disease can occur in one of the three areas in which the organ is divided: supraglottis, glottis and subglottis. A single study was found, with a sample of 59 individuals advanced laryngeal squamous cell carcinoma. GRP78 was not statistically associated with overall survival, but regarding disease-free survival (PFS), univariate analysis showed that low levels of GRP78 expression were associated with worse outcomes, and in multivariate analysis, decreased GRP78 was an independent prognostic factor to predict worse outcomes (KAIRA et al., 2016b). Although, GRP78 was not associated with any other clinicopathological variable assessed (KAIRA et al., 2016b).

HYPOPHARYNGEAL

Are tumors in the deep part of the throat. Like most malignant tumors of the head and neck, statistics show that incidence and mortality have higher rates in men (SUNG et al., 2021).Consisting of a sample of 68 individuals, a single study was found. No clinical or histological variables were statistically related to the levels of GRP78 in tumor tissue. Regarding survival, the low expression of GRP78 was an independent predictive factor for shorter overall survival and progression-free survival in advanced HSCC (KAIRA et al., 2016a). In addition, the low expression of GRP78 was also a predictive factor related to shorter duration of survival after surgical intervention for advanced HSCC (KAIRA et al., 2016a).

SALIVARY GLAND CANCER

Adenoid cystic carcinoma is one of the most common malignant neoplasms of the salivary glands that mainly affects the parotid, submandibular and accessory salivary glands. Two articles were analyzed, including 95 patients. No comparison with normal salivary gland tissue was performed.

The high expression of GRP78 was an important variable for shorter OS and for PFS in univariate analysis, however when a multivariate analysis was performed GRP78 was not a prognostic significant independent predictor (KAIRA et al., 2015). In contrast, Jiang et al. (2012) presented results showing that positive expression of GRP78 was associated with longer overall survival. Jiang et al. (2012) also showed that positive GRP78 expression was associated with the histological growth pattern

tubular/cribiform rather than solid and with lower histological grade (JIANG et al., 2012) corroborating survival findings. Meanwhile, Kaira et al. (2015) found no correlation with histological subtypes (KAIRA et al., 2015). Beyond that, there was no association between GRP78 and age (KAIRA et al., 2015; JIANG et al., 2012) , sex (KAIRA et al., 2015) and gender (JIANG et al., 2012) , tumor site (KAIRA et al., 2015) and tumor size (JIANG et al., 2012).

ESOPHANGEAL

Esophageal carcinoma is one of the main causes of death of neoplasms involving the gastrointestinal tract. Being that the main risk factors are alcoholism, tabagism and human papillomavirus infection (TUSTUMI et al., 2016). Four articles were included in this category, with a total of 413 patients, being 208 adenocarcinomas (LANGER et al., 2008; SLOTTA-HUSPENINA et al., 2013) and 205 squamous cell carcinomas (SCC) (REN et al., 2017; ZHAO et al., 2015). Only two studies compared the expression of GRP78 in tumor tissue with the adjacent normal (REN et al., 2017;LANGER et al., 2008). GRP78 was overexpressed in esophageal SCC tissues (REN et al., 2017). Normal esophageal squamous epithelium showed moderate staining intensity for GRP78 (LANGER et al., 2008).

High GRP78 expression was significantly associated with shorter overall survival in SCC (REN et al., 2017; ZHAO et al., 2015), patients with weak or strong positive GRP78 expression showed significantly poorer survival than patients with negative GRP78 expression (SLOTTA-HUSPENINA et al., 2013). However this association was not investigated for adenocarcinomas.

In esophageal SCC, high GRP78 expression was significantly correlated with positive lymph node metastasis (REN et al., 2017; ZHAO et al., 2015) and advanced tumor stage (REN et al., 2017) .While no association was detected with immunohistochemistry and platin/5-fluorounacil chemotherapy response (SLOTTA-HUSPENINA et al., 2013). In constrat for esophageal adenocarcinomas. GRP78 showed no relation with CTX response (SLOTTA-HUSPENINA et al., 2013) a and early tumors stages was identified (LANGER et al., 2008).

GASTRIC

In addition to gastric cancer being one of the main malignities, it is one of the main causes of cancer death in the world, being the healthy diet, anti- H.pylori therapies, and chemoprevention some of the types of primary prevention for this disease (SITARZ; SKIERUCHA; MIELKO, 2018).This category included six articles, totaling an analysis of 1,581 patients.

Of these six studies, three analyzed the expression of GRP78 in cancerous tissue in comparison with the normal adjacent mucosa (WU et al., 2014; ZHANG et al., 2006; ZHENG; TAKAHASHI; LI, 2008), while the others did not compare with other tissue. GRP78 was overexpressed in the primary tumors and metastatic lymph nodes as compared with that in the adjacent normal gastric mucosa (ZHANG et al., 2006) . GRP78 was highly expressed in gastric adenomas and carcinomas compared with normal mucosa, and higher expression was detected in lymph node metastasis (OGAWA et al., 2017; WU et al., 2014b; YANG et al., 2014; ZHANG et al., 2006; ZHENG; TAKAHASHI; LI, 2008). Moreover, the SRC (Signet ring cell carcinoma) subtype exhibited weaker expression of GRP78 than the well-, moderately- or poorly-differentiated subtypes (ZHENG et al., 2010). However, there was no difference in GRP78 expression between intestinal and diffuse-type carcinomas (ZHENG; TAKAHASHI; LI, 2008)Two articles in this grou compared the overall survival of these patients (OS) (OGAWA et al., 2017; ZHANG et al., 2006), and the multivariate analysis showed that GRP78 is not an independent predictive factor for OS. Although, the survival duration in patients with weak and strong GRP78 expression was inferior when compared with those with negative expression (ZHANG et al., 2006).

GRP78 immunostaining was compared with other prognostic factors and a positive association was detected between high levels of GRP78 and lymph node status (OGAWA et al., 2017; YANG et al., 2014; ZHENG; TAKAHASHI; LI, 2008) infiltration depth, histological grade, disease stage (OGAWA et al., 2017; YANG et al., 2014) T factor, and lymphatic and vascular invasion (OGAWA et al., 2017; ZHENG; TAKAHASHI; LI, 2008).

PANCREAS

Pancreatic cancer is a group of highly aggressive cancers that have as their most common risk factors smoking, overweight and type 2 diabetes (MIZRAHI et al.,

2020). Three articles were found resulting in a sample of 264 patients: 35 samples of solid pseudopapillary tumor (XIE et al., 2016) 180 pancreatic ductal adenocarcinoma (NIU et al., 2015), and 49 pancreatic neuroendocrine tumor (KLIESER et al., 2015). All studies analyzed the expression of GRP78 in tumor tissue compared to normal tissue (KLIESER et al., 2015; NIU et al., 2015; XIE et al., 2016).

Pancreatic adenocarcinomas showed higher expression of this marker in tumor tissues (NIU et al., 2015), whereas conflicting findings were detected regarding pancreatic neuroendocrine tumors (pNET), while higher expression of GRP78 was detected in one study (XIE et al., 2016) a second study (KLIESER et al., 2015), failed to detect significant differences. In contrast the solid pseudopapillary tumor showed decreased expression of GRP78 in comparison to normal tissues (KLIESER et al., 2015),

.. Higher expression of BiP was linked to a worse outcome (KLIESER et al., 2015). However, GRP78 association with worse overall survival did not reach statistical significance (KLIESER et al., 2015; NIU et al., 2015). In addition, the expression of GRP78 in the tumor tissue was significantly associated with the tumor stage (KLIESER et al., 2015; NIU et al., 2015), higher T-stages were associated with higher levels of GRP78. For pancreatic neuroendocrine tumors, high GRP78 was also statistically associated with positive lymph nodes, distant metastasis and hormone inactivity as well as increased significantly with the tumor grade (KLIESER et al., 2015).

LIVER

Liver cancer is the third leading cause of cancer death and occurs more in men (SUNG et al., 2021). The most common primary liver cancer is hepatocellular carcinoma (HCC). Among the most common risk factors for liver cancer development are hepatitis B or hepatitis C, fatty liver disease and excessive alcohol. 10 articles were found in our search, totaling a sample of 1015 individuals. In most studies, GRP78 is highly elevated in human HCC tissues compared with normal liver tissues (CHENGQUN et al., 2020; XIONG et al., 2019 ; LUO et al., 2018 ;TANG et al., 2012; AL-RAWASHDED et al., 2010; LIM et al., 2005; LUK et al., 2006; LIU et al., 2020).

The overall survival (OS) in patients with higher expression levels of GRP78 was shorter than those with lower expression levels of GRP78 (CHENGQUN et al., 2020; FENG et al., 2019; LIU et al., 2020; LUO et al., 2018; XIONG et al., 2019) and

only Lee et al. (2013) presented a different result, showing that expression of GRP78 was not associated with OS in HCC (LEE et al., 2013) and GRP78 levels were also not associated with longer time to recurrence (TTR) (LEE et al., 2013).

Among the main clinical parameters analyzed, the results are controversial, while some articles show that GRP78 expression was associated with cirrhosis (CHENGQUN et al., 2020) larger tumor size (CHENGQUN et al., 2020; LIM et al., 2005; LUO et al., 2018; XIONG et al., 2019) vascular invasion (LIM et al., 2005; LUO et al., 2018; XIONG et al., 2019) and TNM stage (LUO et al., 2018) others found no such association, demonstrating that GRP78 was not correlated with cirrhosis (LEE et al., 2013) tumor size (LEE et al., 2013) and TNM stage (LEE et al., 2013; AL RAWASHDED et al., 2010; LUK et al., 2006). When the parameter was histological, GRP78 expression was associated with poor differentiation (CHENGQUN et al., 2020) (LIU et al., 2020; LIM et al., 2005) however there was no correlation between GRP78 staining intensity and Edmondson-Steiner (AL-RAWASHDEH et al., 2010; LEE et al., 2013).

COLORECTAL

Colorectal cancer is a malignant tumor that settles in the rectum of the large intestine. Worldwide, colorectal ranks third in terms of incidence and second in terms of mortality (SUNG et al., 2021). Genetic and environmental factors such as family history and diet are among the main risk factors (WEITZ et al., 2005). 6 studies were found, with a sample of 786 individuals. Two studies compared tumor and normal samples and showed higher expression of GRP78 was detected in tumor tissue when compared with their adjacent normal tissue (THORNTON et al., 2013; ZHANG; GUAN; ZHOU, 2012).

Among the studies that analyzed overall survival (OS) (LEE et al., 2015; MHAIDAT et al., 2015; THORNTON et al., 2013) controversial findings were retrieved: while Lee et al. (2015) observed high GRP78 correlated with decreased recurrence-free and OS, the opposite was detected by Thornton et al. (2013) where increased OS was associated with high GRP78 expression. Meanwhile, no significant association was detected between survival and GRP78 immunoreactivity score by Mhaidat et al. (2015) in the first (MHAIDAT et al., 2015), however this study assessed GRP78

staining in cell plasma membrane, whereas the other two detected cytoplasmic staining.

The relationship of GRP78 levels and response to treatment was assessed in the same 3 studies (LEE et al., 2015; MHAIDAT et al., 2015; THORNTON et al., 2013) .Two of them showed that higher GRP78 was related with worse response to chemo and radiotherapy (LEE et al., 2015; MHAIDAT et al., 2015) . However, tumors with higher levels of GP78 in plasma cell membranes presented better responses for fluoropyrimidine-based chemotherapy (THORNTON et al., 2013).

When the parameter was the colorectal (CRC) stage, no differences were found between the expression of GRP78 and CRC stage II and stage III (RYAN et al., 2016). Controversy, the expression of GRP78 increased with the progression from the initial stages to the advanced stages of CRC in another two studies (MHAIDAT et al., 2015; THORNTON et al., 2013).

Controversial findings were also observed when the parameter was histological differentiation, no correlation could be found between GRP78 expression and well, moderate, poor, and unrecorded differentiation (LEE et al., 2015; THORNTON et al., 2013). However, in another research, GRP78 showed higher expression in low differentiation colorectal cancer when compared to modest and high differentiation (ZHANG; GUAN; ZHOU, 2012).

Regarding clinical parameters, stand out the difference between immunoreactivity score and both T category (MHAIDAT et al., 2015) and also the GRP78 expression elevated in cancer tissue correlated with depth of invasion (THORNTON et al., 2013). The samples that showed lower expression of GRP78 had lower levels of recurrence (LEE et al., 2015). The association among high GRP78 and lymph node and distant metastasis was reported in only two studies (MHAIDAT et al., 2015; ZHANG; GUAN; ZHOU, 2012), one detected positive association with lymph node metastasis ZHANG; GUAN; ZHOU, 2012), while the other detected no correlation with lymph and distant metastasis when plasma cell membrane GRP78 staining was investigated (MHAIDAT et al., 2015).

MELANOMA

Melanoma is a cancer originated from melanocytes proliferation and represents the neoplasm with a worse prognosis among skin cancers, with higher incidence and mortality in men worldwide (SUNG *et al.*, 2021). Due to its genotoxic effect, exposure to ultraviolet rays is the main risk factor (RASTRELLI et al., 2014). Four articles were found, totaling a sample of 355 individuals. GRP78 expression was compareded among benign naevi, primary tumors and metastatic tumors (GUAN et al., 2015; ZHUANG et al., 2009a) showing that its greatest expression was associated with the progression of melanoma.

When GRP78 staining was associated with the overall survival (OS) outcome (PAPALAS et al., 2009; SHIMIZU et al., 2017;ZHUANG et al., 2009), increased expression was associated with poorer OS (KAIRA et al., 2016; PAPALAS et al., 2009; ZHUANG et al., 2009) and Progression-free survival (PFS) (SHIMIZU et al., 2017) and disease-free survival (ZHUANG et al., 2009) however it was not an independent predictor of OS (ZHUANG et al., 2009) .In addition, higher expression of GRP78 was associated with tumor thickness (SHIMIZU et al., 2017; ZHUANG et al., 2009), disease staging (SHIMIZU et al., 2017) depth of invasion (PAPALAS et al., 2009), vascular invasion and neural invasion (ZHUANG et al., 2009) and mitotic index (SHIMIZU et al., 2017; ZHUANG et al., 2009).

PROSTATE

Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men (SUNG et al., 2021). With a total of 536 samples of individuals, 3 articles were analyzed (DANESHMAND et al., 2007; POOTRAKUL et al., 2006; TAN et al., 2011). When comparing tumors with control tissues, GRP78 levels in prostate cancer tissue was significantly higher than benign prostatic hyperplasia control (DANESHMAND et al., 2007; TAN et al., 2011).

In addition, when the topic is survival, studies showed that the risk of recurring or dying was greater for patients with tumors that expressed high levels of GRP78 compared with patients with tumors that expressed low levels of GRP78, even after adjusting for known predictors of outcome, like age (DANESHMAND et al., 2007; POOTRAKUL et al., 2006), prostatic specific antigen measurements (POOTRAKUL et al., 2006) and Gleason score (DANESHMAND et al., 2007;POOTRAKUL et al., 2006).

Moreover, the percentage of tumor cells expressing Grp78 was strongly associated with castration-resistant status (TAN et al., 2011; POOTRAKUL et al., 2006). Besides, Tan *et al* (2011) studied the membranous androgen receptor (AR) expression and showed that it was particularly associated with GRP78 expression, in summary, up-regulated GRP78 expression was associated with shorter disease-specific survival in patients with AR+ tumors when compared with AR- tumors (TAN et al., 2011). A significant relation among high levels of GRP78 and resistance to castration treatment was detected (TAN et al., 2011; POOTRAKUL et al., 2006).

Although an important association with resistance to treatment and overall survival was reported in prostate cancer, one study investigated and found no relation with other clinico-pathological features such as age, preoperative PSA levels, pathology stage and Gleason grade (DANESHMAND et al., 2007).

URINARY TRACT TUMORS

The causes of kidney cancer, as in most tumors, are not yet fully understood. Kidney cancer is on the list of the ten types of cancer that kill the most. Both in incidence and mortality, it affects more men (SUNG et al., 2021). The sample consists of 337 individuals, being 114 ccRCC and 223 RCC analyzed in a set of three articles. When compared to non-neoplastic renal tissue, GRP78 was not overexpressed in clear cell renal cell carcinoma (ccRCC) (SHEN et al., 2019).However, GRP78 was overexpressed in RCC when compared to normal tissue in a study by Wang *et al.* (2017). Two studies with RCC showed that the highest levels of GRP78 expression was associated with the highest grade (WANG et al., 2017; KURODA et al., 2011) and lymphovascular invasion (KURODA et al., 2011), while Shen *et al.* (2019) found no association using either quantification method for ccRCC samples (SHEN et al., 2019).

When analyzing survival in RCC, the results were similar, high GRP78 expression was associated with shorter overall survival time (WANG et al., 2017), lower disease-specific survival (KURODA et al., 2011) and less progression-free survival (KURODA et al., 2011). Furthermore, higher levels of GRP78 expression were associated with TNM stage (WANG et al., 2017) and advanced T stage (KURODA et al., 2011). The study assessing ccRCC did not investigate the relation among GRP78 and survival (SHEN et al., 2019).

Cancer of the ureter involving the upper tract is relatively uncommon (FROEMMING et al., 2018). Also two articles were retrieved for cancer ureter, with a sample of 179 individuals. The highest expression of GRP78 is related to nuclear grade by Park et al. (2013 while in the study by Uematsu et al. (2009), there is a specific association with low grade in invasive tumours (PAPALAS et al., 2009). Both studies showed that there is no association between GRP78 levels and age (PARK et al., 2013; UEMATSU et al., 2009) sex (PARK et al., 2013; UEMATSU et al., 2009) and stage (PARK et al., 2013; UEMATSU et al., 2009). Regarding survival, when analyzed bladder recurrence, the recurrence rate was higher in cases where the GRP78 was overexpressed, and associated with that, the survival rate was lower in the GRP78 overexpression group (PARK et al., 2013). Contraversely, Uematsu *et al.* (2009) showed that overexpression of GRP78 improved the disease-free survival rate and did not change the overall survival rate (UEMATSU et al., 2009).

BREAST

Breast cancer is the most common cancer in the world, corresponding for 12% of all new annual cancer cases worldwide (SUNG et al, 2020). The most common risk factors for this disease are being a woman, age over 40 and the familial history of first-degree relatives with breast cancer (KAMIŃSKA et al., 2015).

In this category, 12 articles were included and totaled 1096 samples analyzed. From all of the studies, only three compared tumor tissue with normal tissue (DÉRY et al., 2013; TANG et al., 2018; WANG et al., 2016). GRP78 is highly expressed in breast cancer samples (BARTKOWIAK et al., 2015; TANG et al., 2018). Positive GRP78 staining was detected in 52.6 % (ZHENG et al., 2014), 60,4% (LEE et al., 2011) 67% (LEE et al., 2006) 47.89% (WANG et al., 2016) and 93,3% (LÓPEZ-MUÑOZ; CORRES-MOLINA; GARCÍA-HERNÁNDEZ, 2020)of tumors. Moreover, two studies found a positive and significant association among GRP78 levels and the proliferation marker Ki-67 levels (YANG et al., 2020a; YERUSHALMI et al., 2015).

GRP78 overexpression in cancer patients suggested poorer overall survival (CHEN et al., 2015; TANG et al., 2018; YANG et al., 2020a) and poorer disease-free survival rates (TANG et al., 2018; YANG et al., 2020a; ZHENG et al., 2014). Beyond that, GRP78 expression was associated with lower overall survival in Triple-negative

breast cancer (TNBC) (WANG et al., 2016; YANG et al., 2020), in addition to being associated with poor clinical outcomes (YANG et al., 2020).

The ability to predict treatment response of GRP78 for cancer patients was investigated. Response to treatment seems to depend on GRP78 cell localization (cytoplasmic or membrane) and is also dependent on the type of chemotherapy used. It was detected an association between GRP78 positivity and shorter time to recurrence (TTR) in patients treated with Adriamycin-based adjuvant chemotherapy, and subgroup analysis reveals that the hazard ratio (HR) for the GRP78-positive group increased significantly among patients who did not receive further taxane treatment (LEE et al., 2006) Moreover, GRP78 positivity is associated with shorter recurrence-free survival following doxorubicin-based treatment alone (LEE et al., 2011).

In contrast, positive cell membrane GRP78 expression was associated with an improved DFS and a trend for a superior response to chemotherapy was observed for patients receiving either anthracycline- and taxane-based regimens or Trastuzumab (YERUSHALMI et al., 2015) .Additionally, pre-treatment GRP78 cytoplasmic or cell membrane overexpression was not a predictor of overall (BAPTISTA et al., 2011; LEE et al., 2006) or disease-free survival (BAPTISTA et al., 2011) of patients receiving anthracycline-based adjuvant chemotherapy (BAPTISTA et al., 2011) or taxane (LEE et al., 2006).

In addition, GRP78 expression was associated with tumor differentiation grade in most of the studies which assessed this correlation, poorly differentiated and high-grade tumors showed higher GRP78 levels (BARTKOWIAK et al., 2015; CHEN et al., 2015; DÉRY et al., 2013), whereas Lee et al. (2011) failed to find significant association. Higher expression of GRP78 indicated more malignant distant metastasis (CHEN et al., 2015; TANG et al., 2018), and distant metastases was also positive for GRP78 (BARTKOWIAK et al., 2015; YANG et al., 2020). In line with these previous findings, GRP78 was also associated with lymph vascular invasion (WANG et al., 2016) but not in Lee et al. (2011) study (LEE et al., 2011). In TNBC GRP78 expression was significantly associated with invasive, proliferation and lymph node status (YANG et al., 2020). Controversial findings were observed regarding association with hormonal receptor status. Increased expression of the progesterone receptor was positively associated with GRP78 in one study (70, and a inverse correlation was detected with ERBB2 overexpression (BAPTISTA et al., 2011) whereas Lee et al.

(2011) did not detect statistical association among GRP78 and ER/PR or HER2/neu status (LEE et al., 2011).

GYNECOLOGICAL

OVARIAN

Ovarian cancer is a common type of gynecological cancer, with a family history of the disease being one of the most common risk factors. Despite its low prevalence, it has a high mortality and one of the worst prognosis (MOMENIMOVAHED et al., 2019).Two articles were analysed, totalizing 492 samples (HUANG; LIN; LEE, 2012; SAMANTA et al., 2020). GRP78 is highly expressed in ovarian cancer compared to normal tissues (HUANG; LIN; LEE, 2012; SAMANTA et al., 2020). The comparison among benign and malignant resulted in controversial results, Huang et al. (2012) found that compared with the benign ovarian tumors, GRP78 was highly expressed in Epithelial Ovarian Carcinomas, whereas Samanta et al. (2020) found no statistical difference for this comparison.

The same situation was observed regarding overall survival, while Huang et al. (2012) found that the high GRP78 expression group had a significantly worse overall survival (SAMANTA et al., 2020), whereas Samanta et al. (2020) found no statistical association for this comparison (HUANG; LIN; LEE, 2012) GRP78 expression was correlated with early tumor stages Stages I and III in one study (SAMANTA et al., 2020). But, GRP78 expression was not associated with any other clinicopathologic parameters (HUANG; LIN; LEE, 2012).

ENDOMETRIAL

Endometrial cancer (EC) is the most common gynecological type of cancer in the United States (BURKE et al., 2014), with obesity being the most well-known and well-established risk factor for this disease (YE et al., 2016) Four articles were analysed, totalizing 736 samples (GRAY et al., 2013; GUO et al., 2018; MATSUO et al., 2013; TENG et al., 2013) GRP78 expression was consistently higher in tumoral tissues than normal tissues (GRAY et al., 2013; GUO et al., 2018; MATSUO et al., 2013; TENG et al., 2013). Moreover, the positive rate of GRP78 was higher in high risk EC tissue than in low-risk EC (TENG et al., 2013).

Patients with high GRP78 expression had worse prognosis than those with low expression of these proteins (GUO et al., 2018). Patients with advanced disease with tumoral GRP78 expression relatively higher than adjacent normal endometrium presented shorter time to progression compared to those with the same or decreased tumoral GRP78 expression relative to normal endometrium (MATSUO et al., 2013). GRP78 expression was also positively correlated with FIGO stage, pathological type, histological grade, and lymph node metastasis (GUO et al., 2018). In addition, visceral adipocyte GRP78 protein levels of patients with EC was also investigated and interestingly, high visceral adipocyte GRP78 expression was positively correlated with advanced-stage disease and deep myometrial invasion, decreased disease-free survival (DFS) in multivariate analyses (MATSUO et al., 2013).

LUNG

Lung cancer is responsible for 11,4% of new cancer cases each year, being one of the main causes of mortality in several countries in the world (SUNG et al., 2021). Tobacco use is the main risk factor, meanwhile genetic susceptibility, poor diet, occupational exposures, and air pollution are also considered risk factors for this disease (MALHOTRA et al., 2016).

There are different types of lung cancer. Non-small-cell lung carcinoma (NSCLC) is any type of epithelial lung cancer other than small-cell lung carcinoma (SCLC). The most common types of NSCLC are squamous-cell carcinoma, large-cell carcinoma, and adenocarcinoma, but several other types occur less frequently. A few of the less common types are pleomorphic, carcinoid tumor, salivary gland carcinoma, and unclassified carcinoma (ZAPPA; MOUSA, 2016).

In this review five of them were described: Non-small cell lung cancer (NSCLC, n=1.240); Pu(IMAI et al., 2017; KIM et al., 2012; KWON et al., 2018; LEE et al., 2019; WANG et al., 2020; WU et al., 2014; YU; LUO; LIU, 2016)lmonary pleomorphic carcinoma (PPC) n=105 (IMAI et al., 2019); Lung adenocarcinoma (LA) n=208 (YAMADA; NIISATO, 2016) Bronchioloalveolar carcinoma (BAC) n=21 (KIM et al., 2012) and the precursor lesions atypical adenomatous hyperplasia (TAH) (KIM et al., 2012). The sample consists of ten papers totalizing 1.715 samples. Six of them compared the expression of GRP78 in NSCL tumor tissue and in normal tissue (KIM et al., 2012; KWON et al., 2018; WANG et al., 2020; WU et al., 2014; YAMADA;

NIISATO, 2016; YU; LUO; LIU, 2016), and have found higher levels in tumor tissue in comparison to normal tissue.

When different subtypes of NSCLC were compared, most of the studies have found no significant differences regarding GP78 expression (LEE et al., 2019; WANG et al., 2020; WU et al., 2014a; YU; LUO; LIU, 2016) . Kwon et al (2018), on the other hand, detected significantly higher levels of GRP78 in lung adenocarcinomas than squamous cell carcinomas. Whereas the GRP78 positivity rate was significantly higher in the squamous cell carcinoma group than in the adenocarcinoma group in the Imai et al. (2017) study .

Most of the studies showed a positive association of higher levels of GRP78 and worse prognosis (KWON et al., 2018; WANG et al., 2020; YAMADA; NIISATO, 2016; YU; LUO; LIU, 2016). When the evaluated parameter was survival, for patients with lower expression of GRP78, the survival rate was higher (WANG et al., 2020). In patients with LA, higher GRP78 was also associated significantly with shorter disease-free survival (KWON et al., 2018) and shorter survival times (YU; LUO; LIU, 2016). Multivariate analysis confirmed that GRP78/BiP expression was an independent factor for predicting poor progression-free survival and overall survival in patients with stage I disease (IMAI et al., 2017). In LA cases, GRP78 higher expression was significantly correlated with poor outcomes (YAMADA; NIISATO, 2016). Multivariate analysis identified GRP78 as significant independent markers for predicting worse prognosis (IMAI et al., 2019). Paradoxically, Uramoto et al., (2004) studying a mixed sample of 132 specimens showed that lung cancer patients with a positive Grp78 expression tended to show a better prognosis than those with a negative Grp78 expression. In addition, a multivariate analysis of the clinicopathologic characteristics of lung cancer indicated a positive expression of Grp78 to be a significant factor for predicting a favorable prognosis (URAMOTO et al., 2005) and and for adenocarcinomas (IMAI et al., 2019). Lee et al (2019) failed to detect any significant association regarding Recurrence-free survival and GRP78 (LEE et al., 2019).

In addition, elevated GRP78 expression was significantly associated with N factor and pathological stage (IMAI et al., 2019; YU; LUO; LIU, 2016), pathologic TNM status (KIM et al., 2012; WU et al., 2014; YU; LUO; LIU, 2016), pleural invasion, lymphatic permeation, vascular invasion, cell proliferation, p-mTOR phosphorylation,

Ki67, CD34 (IMAI et al., 2017), low pathologic T stage (KIM et al., 2012). Some studies have not found a positive association with clinicopathological parameters(IMAI et al., 2017, 2019; KWON et al., 2018; URAMOTO et al., 2005; WANG et al., 2020).

LYMPOPROLIFERATIVES

LYMPHOMA

Lymphoma is a type of cancer that affects the body's defense cells, and can be subdivided into Hodgkin or non-Hodgkin. Both types have a higher incidence and mortality rate in men (SUNG et al., 2021). Two articles were analyzed, one assessing 156 samples of Hodgkin Lymphomas e one assessing different types of non-Hodking lymphomas: 43 Diffuse Large B-Cell Lymphoma (DLBCLs), 13 follicular lymphomas (FL), 10 marginal zones (MZL), 8 Mantle cell lymphoma (MCLs), 13 T-cell Lynphomas (TCLs) of varying subtypes, 3 chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), 2 post-transplant lymphoproliferative disorders (PTLD).

Aggressive non-Hodgkin lymphomas (DLBCL, MCL Ki67>30%, TCL, and PTLD) were more likely (92%) to express GRP78 when compared to and indolent lymphomas (SLL/CLL, FL, MZL) (50%)(AMENGUAL et al., 2015) The overall survival rates were higher in non-Hodgkin lymphoma patients with lower levels of GRP78 expression (AMENGUAL et al., 2015). Regarding Hodgkin lymphomas Chang et al. (2011) have not detected a relationship between GRP78 expression and overall survival, the expression of any ER signals did not bear prognostic significance (CHANG et al., 2011).

MYELOMA

Multiple myeloma is a cancer that affects the bone marrow. Their incidence and mortality rates are higher in men (SUNG et al., 2021).The sample consisted of 96 individuals, out of a total of 3 articles. Except for Steinner et al. (2017) study, which found no difference among samples regarding staining intensity and localization of GRP78, the greater the disease progression, the higher the GRP78 levels (ADOMAKO et al., 2015; LEO et al., 2016). GRP78 was also elevated in patients with drug-resistant extramedullary disease (LEO et al., 2016). As for disease progression, it is suggested that there is a correlation between higher levels of GRP78 and progressive disease (ADOMAKO et al., 2015), although sample size was limited.

SNC

NEUROBLASTOMA

Neuroblastoma is a type of cancer common in children and adolescents. Although rare, it is very aggressive and related to a poor outcome (WHITTLE; WILLIAMSON; RUSSELL, 2017). Two articles were selected, one assessing only olfactory neuroblastoma (ONB) n=20 (WEINREB et al., 2009), and one assessing different neuroblastomas (n=68), mainly from adrenal (n=37) and the remaining were extra-adrenal non-specified location (HSU et al., 2005). None of them compared the expression of GRP78 in other tissues in addition to the tumor.

GRP78 expression was considered weak in 90% olfactory neuroblastoma cases (WEINREB et al., 2009). Otherwise, others neuroblastic tumors showed positive GRP78 expression in 58,8% (HSU et al., 2005). For both studies, it was observed that patients with positive GRP78 expression did have better survival than those with negative expression (HSU et al., 2005; WEINREB et al., 2009). Moreover, positive GRP78 expression was an independent prognostic factor and predicted better survival in patients with either undifferentiated or differentiated histologies (HSU et al., 2005). However, it failed to predict recurrence free survival in olfactory neuroblastomas, and showed no difference between the low- (1 and 2) and high-grade (3 and 4) ONBs.

In addition, positive GRP78 expression strongly correlated with higher histological differentiation and early clinical stages, but inversely correlated with MYCN (Proto-Oncogene, BHLH Transcription Factor) amplification (HSU et al., 2005).

ASTROCYTIC TUMORS

Astrocystic tumors are the most common types of brain cancer (RIEMENSCHNEIDER; REIFENBERGER, 2009). Among different types of tumors, glioblastoma (grade IV astrocytic tumor) is the most common malignancy in the brain, with more than 80% of cases affecting older age. With an average survival rate of 15 months, it is still a disease with no cure and with an invasive treatment (THAKKAR et al., 2014).

Four articles were analysed, totalizing 299 samples (PEÑARANDA-FAJARDO et al., 2019; RAMÃO et al., 2012; YANG et al., 2020b; ZHANG et al., 2010)**.** Three of them compared the expression of GRP78 in tumoral and normal tissues (RAMÃO et al., 2012; YANG et al., 2020b; ZHANG et al., 2010) and have observed that GRP78

was up-regulated in astrocytoma compared with normal astrocytic tissue. Moreover, higher levels were detected in higher tumor grades (ZHANG et al., 2010).

No significant association between GRP78 expression in the GBM specimens and OS was detected(PEÑARANDA-FAJARDO et al., 2019). However, immunoreactivity of GRP78 was shown to be inversely correlated with PFS of recurrent GBM patients using both univariate and multivariate Cox regression analyses (ZHANG et al., 2010).

OTHERS

MESOTHELIOMA

Mesothelioma is a type of aggressive cancer that is located in the mesothelium, a thin tissue that covers the body's internal organs. Worldwide, mortality rates are higher in men (SUNG et al., 2021). Only one article was found, with a sample of 153 individuals (DALTON et al., 2013). Two parameters were evaluated, histological and survival. GRP78 expression was increased in the epithelioid histological subtype in comparison to the biphasic and sarcomatoid subtypes and also with mesothelial differentiation. There was no association between GRP78 and overall survival (DALTON et al., 2013).

ADVANCED THYMIC CARCINOMA

Thymic carcinomas are rare invasive thymic epithelial tumors associated with a poor prognosis (ENG et al., 2004). With a sample of 34 individuals, one paper was found. Among the clinical (age, gender, smoking, postoperative recurrence, stage, long diameter of primary tumor, performance status, metastatic site) and pathological variables investigated, none was associated with the level of GRP78 (MIURA et al., 2017) When the evaluated parameter was overall survival (OS), the results showed that patients with high level of GRP78 expression had longer overall survival compared to those with a low level (46.2 vs. 16.8 months), being considered an independent prognostic factor for prolonged OS (MIURA et al., 2017). Also, no significante association with response to CTX was detected (MIURA et al., 2017).

DISCUSSION

Biomarkers for cancer prognostication are extremely important tools to improve personalized decision-making and to predict treatment response. To achieve this purpose a biomarker must be readily applicable. An additional advantage would be a biomarker available for the largest possible number of different tumors. This feature improves reproducibility and reduces costs. Therefore, GRP78 immunohistochemistry levels assessment is a promising alternative, since this protein is highly expressed in cancer cells and it is responsible for a pro-survival signaling.

Several studies that analyzed and compared the expression of GRP78 in tumor tissue and adjacent non-neoplastic tissue showed that the expression of the GRP78 protein is higher in tumor tissue in the gastric (OGAWA et al., 2017; WU et al., 2014b; YANG et al., 2014; ZHANG et al., 2006; ZHENG; TAKAHASHI; LI, 2008), colorectal (KUO et al., 2013; THORNTON et al., 2013; ZHANG; GUAN; ZHOU, 2012) prostate (DANESHMAND et al., 2007; TAN et al., 2011), renal (CHENGQUN et al., 2020; LIM et al., 2005; LIU et al., 2020; LUK et al., 2006; LUO et al., 2018; XIONG et al., 2019; ;TANG et al., 2012; AL-RAWASHDED et al., 2010), breast (TANG et al., 2018; WANG et al., 2016), oral (HUANG et al., 2010; XIA et al., 2014) nasopharynx (FENG et al., 2018; YI et al., 2016), astrocytic (YANG et al., 2020; RAMÃO et al., 2012; ZHANG et al., 2010) ovarial (HUANG; LIN; LEE, 2012; SAMANTA et al., 2020) and endometrial cancers (GRAY et al., 2013; GUO et al., 2018; MATSUO et al., 2013; TENG et al., 2013). Increased amount of GRP78 in tumor tissue is explained because of different conditions within tumor microenvironment: neoplastic cells present higher levels of protein synthesis due to higher proliferation status; genetic mutations and genomic rearrangements resulting from the tumor development result in accumulation of misfolded mutated proteins requiring the chaperone to improve this function; tumor microenvironment usually is characterized by stressful conditions as hipoxia, acidosis and glucose privation resulting in ER stress (GIAMPIETRI et al., 2015a; HAZARI et al., 2016).

Few exceptions have detected opposite findings. Whereas GRP78 was found in greater amounts in pancreatic cancer samples (KLIESER et al., 2015; NIU et al., 2015), an exception is made regarding the solid pseudopapillary tumor (XIE et al., 2016), which presented lower levels of GRP78 in comparison to adjacent normal tissues. In the case of kidney cancer, controversial findings were detected, the GRP78

was higher in the RCC when compared to the non-neoplastic tumor tissue (WANG et al., 2017), different from the results presented by Shen et al. (2019) in which there was no significant difference in protein expression between the non-tumor tissue and the clear cell variant of RCC.

Corroborating the above mentioned findings, when the comparison was between primary tumors and metastatic tumors, or versus low grade versus aggressive tumors, higher levels of GRP78 were found in metastatic melanoma (GUAN et al., 2015; ZHUANG et al., 2009) versus primary tumors, and in aggressive non-Hodgkin's lymphomas versus indolent lymphomas (AMENGUAL et al., 2015). However, in the esophageal tumor, GRP78 showed higher levels in tumors in the initial stage compared to normal tissue and tumors in advanced stages (LANGER et al., 2008). The discrepancies between results may reflect a different GRP regulation depending from the tumor type or the heterogeneity of the assessed studies.

It was demonstrated that GRP78 plays an important role in tumor cell proliferation, angiogenesis, metastasis and resistance to anticancer drugs. In addition, this chaperone is overexpressed in several types of tumors (LUO; LEE, 2013). Among the 91 studies analyzed, the GRP78 was overexpressed and was associated with greater aggressiveness in 61 (67%) articles, that is, less overall survival, disease free survival or worse response to treatment.

There was a small subgroup where a higher expression of GRP78, was associated with a better prognosis, among these nine different types of cancer (neuroblastoma, laryngeal, hypopharyngeal, advanced thymic carcinoma, non-hodgkin lymphoma, urothelial carcinoma, adenoid, colorectal, and ung adenocarcinoma) have been found, totaling ten articles (AMENGUAL et al., 2015; HSU et al., 2005; JIANG et al., 2012; MIURA et al., 2017; THORNTON et al., 2013; UEMATSU et al., 2009; URAMOTO et al., 2005; WEINREB et al., 2009; KAIRA et al., 2016a; KAIRA et al., 2016b). However, for these results to be confirmed, it will be necessary a larger sample, since this result was found in only one study of each type of cancer, with the exception of neuroblastoma, which comprised both studies assessing (HSU et al., 2005; WEINREB et al., 2009). A possible explanation for these controversial findings is that for tumors originating from highly secretory cells or from cells with high protein synthesis (SZEGEZDI et al., 2006), high basal levels of GRP78

are expected and tumor cells maintaining high GRP78 may denote well differentiated tumors.

As shown in the results, in face of cellular stress caused by the tumor environment, the regulatory pathway activates a response leading to GRP78 protein overexpression, suggesting that GRP78 activation in these cases results in a tumor survival advantage. Not yet well understood in the literature, this mechanism seems to influence the chemotherapy treatment response. Tumor resistance to chemotherapy drugs has become an enormous challenge in the treatment of various types of cancer (WANG et al., 1999). As a consequence, several guidelines have been investigated in order to defeat resistance to chemotherapy in neoplastic treatment (ELFIKY et al., 2020; ROLLER; MADDALO, 2013). Conflicting findings were observed regarding GRP78 levels and response to chemotherapy, suggesting that GRP78 play different roles according to different treatment regimens and according to the type of cancer.

In colorectal cancer, while Mhaidat et al. (2015) showed that higher levels of GRP78 made the chances of the response to chemotherapy treatment lower, using FOLFOX, FOLFOX + Bevacizumab, FOLFOX + FOLFIRI, capecitabin + oxaliplatin (MHAIDAT et al., 2015), Thornton et al. (2013) showed the opposite, in which higher levels of GRP78 were associated with a better chemotherapeutic response, when the treatment was performed with 5-fluorouracil (THORNTON et al., 2013). In contrast, for esophageal tumors with high levels of GRP78 (associated with other chaperon and heat shock proteins) a better response to chemotherapy treatment with cisplatin/oxaliplatin and 5-fluorouracil was observed when compared to tumors that expressed low levels (SLOTTA-HUSPENINA et al., 2013).

GRP78-positive breast tumors were more resistant and showed higher probability of recurrence to treatment to doxorubicin (LEE et al., 2006, 2011; ZHENG et al., 2014). In contrast, GRP78 positivity seems to be associated with higher responsiveness to chemotherapy in patients who received both doxorubicin and taxane treatment (LEE et al., 2006). Later, the same research group published similar results in an independent cohort of taxane-treated breast cancer patients, although the association has not reached statistical significance due to a small sample size (48 patients) (LEE et al., 2011). Considering that GRP78 may play different roles according to different treatment regimens, it was shown that taxanes block microtubules polymerization, which, in turn, may interfere and disrupt the endoplasmic reticulum

organelle and inhibit GRP78 transcription (TERASAKI; REESE, 1994). Therefore, taxanes may have an important recommendation for tumors with high GRP78 levels and resistance to previous treatment.

Besides a role in chemoresistance, in nasopharyngeal cancer, the correlation of increased expression of GRP78 with NPC radioresistance was detected (YI et al., 2016). This can be explained by the anti-apoptotic functions of GRP78, which may result in increased resistance to cell death.

According to the findings reported by this systematic review, Grp78 may have an important role in promoting cell invasion and metastasis (LU; LUO; ZHU, 2020) Twenty-three of articles studied observed that there was a relationship between high expression of Grp78 and metastasis in n lung (IMAI et al., 2019; YU; LUO; LIU, 2016), melanoma (SHIMIZU et al., 2017) gastric (OGAWA et al., 2017; YANG et al., 2014; TAKAHASHI et al., 2011),pancreas (KLIESER et al., 2015; REN et al., 2017) colorectal (ZHANG; GUAN; ZHOU, 2012) liver (LUO et al., 2018) breast (TANG et al., 2018; BARTKOWIAK et al., 2015; YANG et al., 2020a) , urinary (WANG et al., 2017a), oral (XIA et al., 2014) nasopharyngeal(YI et al., 2016) endometrial (GUO et al., 2018) cancers. *In vitro* studies with different cell cancer models have shown mechanistically interplays among GRP78 and metastasis pathways. In an *in vitro* study, Sun et al. (2019) showed in lung adenocarcinoma cells that under hypoxia conditions there is 1,36-fold increase in GRP78 intensity in the cytoplasm and cell membrane when compared to normoxia conditions, and this induction was related to the epithelial-mesenchymal transition (EMT). EMT was responsible for the inhibition of E-cadherin expression and increased fibronectin and vimentin, thus increasing tumor metastasis ability. When GRP78 was inhibited the EMT process was prevented.

In addition, for esophageal carcinoma cells (ESCC), it was seen that UTP14A increased expression fostered cell proliferation and migration, and this was due to PERK/elf2/GRP78 pathway activation (LI et al., 2021). In hepatocellular carcinoma, it was shown that GRP78 regulates HOXB9 through the Wnt signaling pathway by chaperoning low-density lipoprotein receptor-related protein 6 (LRP6). GRP78 knockdown reduced HOXB9 levels and inhibited invasion and metastasis of HCC cells (XIONG et al., 2019). Confirming these results, down-regulation of GRP78 significantly inhibited the metastatic and proliferative ability of anaplastic thyroid

cancer cells. In this in vitro model it was detected that GRP78 was related to extracellular matrix remodeling (ZHAO et al., 2020).

GRP78 is a protein found, in most cases, in the cellular endoplasmic reticulum (ER), however, its presence in the cell plasma membrane (CPM) has already been reported (LI; LEE, 2006). Despite this, the presence of GRP78 in the CPM, as well as its functions, are still not well understood. When this chaperone is moved from the ER to the PM, different functions are observed, such as acting as a receptor for several proteins that can modulate cell proliferation (GONZALEZ-GRONOW et al., 2009). In addition, GRP78 in CPM was associated with increased angiogenesis, thus contributing to tumor progression. Therefore, GRP78 presents itself as a regulator of tumor signaling (NI; ZHANG; LEE, 2011) and an important cellular target for anticancer therapy (ARAP et al., 2004)**.**

In the present review, GRP78 was found in 48,3% of cases in the cytoplasm, 2.2% in the CPM, 9,8% in both CPM and cytoplasm, in the cytoplasm and nucleus in 3,3%, while in 30,7% of the cases the cell compartment was not informed. It was observed that in cases where this chaperone was found in CPM (MHAIDAT et al., 2015; STEINER et al., 2017), no difference among samples regarding staining intensity and localization of GRP78 was found (STEINER et al., 2017), but higher GRP78 was related with worse response to chemo and radiotherapy (MHAIDAT et al., 2015). In cases where the staining occurred in the cytoplasm, in most cases, the overexpression of GRP78 was related to lower OS, DFS and tumor progression.Regarding the other cell locations, no clear associations emerged since few studies. In cases where GRP78 was found in both CPM and cytoplasm, there was no clear association regarding the presence of GRP78 in these compartments and more aggressive outcomes, since 4 articles (KAIRA et al., 2016b; MIURA et al., 2017; YERUSHALMI et al., 2015; KAIRA et al., 2016a) showed a better prognosis when present in CPM and cytoplasm, 5 studies had a worse prognosis (IMAI et al., 2017; LIN et al., 2010; OGAWA et al., 2017; SHIMIZU et al., 2017; KAIRA e al., 2016) and in the remaining 3 studies there was no relationship with the outcome (BAPTISTA et al., 2011; KAIRA et al., 2015; SHEN et al., 2019).

When observed in the nucleus, GRP78 might play a role against DNA damage induced apoptosis through a distinct regulatory mechanism in the nucleus (NI; ZHANG; LEE, 2011). In this review, GR78 was found in the cytoplasm and nucleus in 5 studies

(JIANG et al., 2012; LIM et al., 2005; TAN et al., 2011; WU et al., 2014; YI et al., 2016), considered overexpressed in three (LIM et al., 2005; TAN et al., 2011; YI et al., 2016) of them. While one (WU et al., 2014) did not found any association and 124 was related with better prognosis. Therefore, for these results to be confirmed, it will be necessary a larger sample, where this chaperone is marked on the plasma membrane, since it was found in only 2 works. Besides that, the Immunohistochemistry technique has some limitations such as the difficulty in distinguishing between the cytoplasm and the plasma membrane expression, especially when functions of the antigen are not fully understood (SEIDAL; BALATON; BATTIFORA, 2001).

CONCLUSION

We concluded that Grp78 is a biomarker of tumor prognosis. For most of the studies, 61 manuscripts with 7905 patients, high levels of GRP78 are correlated with worst prognosis (oral, nasopharyngeal, esophageal, gastric, melanoma, pancreas, liver, prostate, urinary tract, breast, endometrial, and astrocytic). In few cases the opposite is expected, as in neuroblastomas, high levels of GRP78 are correlated with better prognosis. The correlation between GRP78 levels and response to treatment was dependent on the type of drug and the type of tumor. Wherefore, there is a need for further studies, which correlate the response to treatment with the GRP78 levels, according to each medications used in the treatment of different tumors. Among the clinico-pathological parameters, an association of GRP78 expression and metastasis arose, suggesting a possible role of this chaperon in favoring invasion and dissemination, which requires further investigation.

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4 CONCLUSÃO

Concluí-se que GRP78 é um bom biomarcador de prognóstico tumoral. Em 61 estudos, com total de 7.905 pacientes, altos níveis de GRP78 estão correlacionados com pior prognóstico (oral, nasofaríngeo, esofágico, gástrico, melanoma, pâncreas, fígado, próstata, trato urinário, mama, endométrio e astrocítico). Em poucos casos , o oposto é esperado, como nos neuroblastomas, em que níveis elevados estão correlacionados com melhor prognóstico. A correlação entre os níveis de GRP78 e a resposta ao tratamento foi dependente do tipo de medicamento e do tipo de tumor. Portanto, são necessários mais estudos que correlacionem a resposta ao tratamento com os níveis de GRP78, de acordo com cada medicamento utilizado no tratamento de diferentes tumores. Dentre os parâmetros clínico-patológicos, surgiu uma associação da expressão de GRP78 e metástases, sugerindo um possível papel desse acompanhante no favorecimento da invasão e disseminação, o que requer maiores investigações.

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APENDICE A – DISTRIBUIÇÃO DOS ESTUDOS EM RELAÇÃO À EXPRESSÃO DE GRP78 NOS TECIDOS TUMORAIS EM RELAÇÃO AOS CONTROLES

	HIGHER EXPRESSION OF GRP78 IN TUMOR TISSUE (TT), PRIMARY (PT) OR METASTATIC (MT) THAN NORMAL TISSUE (NT) OR BENIGN TISSUE (BT) OR PRECANCEROUS TISSUES (PCT)	**HIGHER EXPRESSION OF GRP78 IN NORMAL TISSUE (NT) THAN TUMOR TISSUE (TT)**	**NO STATISTICAL SIGNIFICANCE**
ORAL	Xia et al. (2014) n=46 TT X NT Huang et al. (2010) n=52 TT X NT Lin et al (2010) n=204 TT X PCT Kaira et al. (2016) n = 85 MT X PT	-	-
NASOPHARYNGEAL	Yi et al. (2016) n = 149 TT X NT Feng et al. (2018) n = 92 TT X BT		
HYPOPHARYNGEAL			Kaira et al. (2016a) n = 68
ESOPHAGEAL	Ren et al. (2017) n = 92 TT X NT		
GASTRIC	Zhang et al. (2006) n = 86 TT X NT Ogawa et al. (2017) n = 328 TT X NT Wu et al. (2014b) n = 12 TT X NT Yang et al. (2014) n = 237 TT X NT Zheng; Takahashi; Li (2008) n = 86 TT X NT		
PANCREAS	Niu et al. (2015) n = 180 TT X NT Klieser et al. (2015) n = 49 TT X NT	Xie et al. (2016) n = 35 (SPTP) TT X NT	Xie et al. (2016) n = 35 (PNET) TT X NT
LIVER	Chengqun et al. (2020) n = 89 TT X NT Xiong et al. (2019) n = 106 TT X NT Luo et al. (2018) n = 112 TT X NT Tang et al. (2012) n = 98 TT X NT Al-Rawashded et al. (2010) n = 86 TT X NT		

	Lim et al. (2005) n = 38 TT X NT Luk et al. (2006) n = 67 TT X NT Liu et al. (2020) n = 169 TT X NT		
COLORECTAL	Thornton et al. (2013) n = 396 TT X NT Zhan; Guan; Zhou (2012) n = 198 TT X NT		
MELANOMA	Zhuang et al. (2009a) n = 141 TT X BT Guan et al. (2015) n = 30 MT X PT		
PROSTATE	Daneshmand et al. (2007) n = 153 TT X BT Tan et al. (2011) n = 164 TT X BT		
URINARY TRACT TUMORS	Wang et al. (2017) n = 86 TT X NT		Shen et al. (2019) n = 114
BREAST	Barthkowiak et al. (2015) n = 89 TT XNT Tang et al. (2018) n = 121 TT XNT		Déry et al. (2013) n = 46
OVARIAN	Huang; Lin; Lee (2012) n = 96 TT X NT Samanta et al. (2020) n = 396 TT X NT Huang et al. (2012) n = 96 TT X BT		
ENDOMETRIAL	Gray et al. (2013) n = 260 TT X NT Guo et al. (2018) n = 130 TT X NT Matsuo et al. (2013) n = 227 TT X NT Teng et al. (2013) n = 119 TT X NT		
LUNG	Kim et al. (2012) n = 152 TT X NT Kwon et al. (2018) n = 396 TT X NT Wang et al. (2020) n = 360 TT X NT Wu et al. (2014) n = 40 TT X NT Saito et al. (2016) n= 208 TT X NT		

	Yu; Luo; Liu (2016) n = 89 TT X NT		
LYMPHOMA	Amengual et al. (2015) n= 80 TT X BT		
ASTROCYTIC TUMORS	Ramão et al. (2012) n = 8 TT X NT Wen; Chen; Cheng (2020) n = 28 TT X NT Zhang et al. (2010) n = 115 TT X NT		
TOTAL	48 studies n= 6641	1 study n=35	4 studies n= 263

APENDICE B – RELAÇÃO DE ESTUDOS SELECIONADOS EM RELAÇÃO À SOBREVIDA GERAL E EXPRESSÃO DE GRP78

	HIGHEXPRESSION OF GRP78 and POOR OVERALL SURVIVAL	**HIGHEXPRESSION OF GRP78 and BETTER OVERALL SURVIVAL**	**NO ESTATISTICAL SIGNIFICANCE**
ORAL	Xia, F. et al.,2014 (n=46) / Huanget, T. et al., 2010 (n = 52) / Lin, C. et al., 2009 (n = 204) / Kaira, K. et al., 2016 (n = 85)	-	-
NASOPHARYNGEAL	Feng, X. et al., 2018 (n = 92) / Yi, H. et al., 2015 (n = 149)	-	-
LARYNGEAL	-	Kaira, K. et al., 2016 (n = 59)	-
HYPOPHARYNGEAL	-	Kaira, K. et al., 2016 (n = 68)	-
SALIVARY GLAND CANCER	-	Jiang, L. et al., 2012 (n = 79)	Kaira, K. et al. 2015 (n = 26)
ESOPHAGEAL	Ren, P. et al., 2017 (n = 92) / Zhao, G. et al., 2015 (n = 113)	-	Slotta-Huspenina, J. et al. 2013 (n = 82) / Langer,R. et al. 2008 (n = 126)
GASTRIC	Ogawa, H. et al., 2017 (n = 328) / Wu, J. et al., 2014 (n = 12) / Yang, L. et al., 2014 (n = 237) / Zheng, H. et al., 2007 (n = 487) / Zhang, J. et al., 2006 (n = 86)	-	Zheng, H. et al., 2010 (n = 517)
PANCREAS	Niu, Z. et al., 2015 (n = 180) / Klieser, E. et al., 2015 (n = 49)	-	Xie, J. et al., 2016 (n = 35)
LIVER	He, C. et al., 2020 (n = 89) / Liu, J. et al., 2020 (n = 169) / Xiong, H. et al.,	-	Lee, Y. J. et al., 2013 (n = 190)

	2019 (n = 106) / Feng, Y. et al., 2019 (n = 60) / Luo, C. et al., 2018 (n = 112) / Tang, J. et al., 2012 (n = 98) / Al-Rawashdeh, F. Y. et al., 2010 (n = 86) / Luk, J. M. et al., 2006 (n = 67) / Lim, S. O. et al., 2005 (n = 38)		
COLORECTAL	Zhang, L. Q. et al., 2012 (n = 198) / Mhaidat, N. M. et al., 2015 (n = 68) / Lee, H. Y. et al., 2015 (n = 101)	Thornton, M. et al. 2013 (n = 396)	Ryan, D. et al., 2016 (n = 23)
MELANOMA	Shimizu, A. et al., 2016 (n = 133) / Guan, M, et al., 2014 (n = 30) / Papalas, J. A. et al., 2010 (n = 51) / Zhuang, L. et al., 2009 (n = 171)	-	-
PROSTATE	Tan, S. S. et al., 2011 (n = 164) / Daneshmand, S. et al., 2007 (n = 153) / Pootrakul, L. et al., 2006 (n = 219)	-	-
URINARY TRACT TUMORS	Park, C. H. et al., 2013 (n = 53) / Kuroda, K. et al., 2011 (n = 137) / Wang, C. et al., 2017 (n = 86)	Uematsu, K. et al. 2009 (n = 126)	Shen, K. et al., 2019 (n = 114)
BREAST	Yerushalmi, R. et al., 2015 (n = 19) / Chen, H. et al., 2014 (n = 108) / Wang, J. et al., 2016 (n = 71) / Bartkowiak, K. et al., 2015 (n = 89) / Tang, H. et al., 2018 (n = 121) / Zheng, Y. et al.,	-	Déry, M. A. et al., 2013 (n = 46) / Lee, E. et al. 2006 (n = 127) / Baptista, M.Z. et al., 2011 (n = 106) / Lee, E. et al., 2011 (n = 48) / López-Muñoz,

	2014 (n = 213) / Yanget, C. al., 2020 (n = 179)		E. et al. 2019 (n = 15)
OVARIAN	Soma, S. et al., 2020 (n = 415)	-	Huang. L. et al., 2012 (n = 96)
ENDOMETRIAL	Guo, S. et al., 2018 (n = 130) / Gray, M. J. et al., 2013 (n = 260) / Matsuo, K. et al., 2013 (n = 227) / Teng, Y. et al., 2013 (n = 119)	-	-
LUNG	Wang, J. et al., 2020 (n = 360) / Imai, H. et al., 2019 (n = 105) / Kwon, D. et al., 2018 (n = 369) / Saito, H. et al., 2015 (n = 208) / Yuet, D. al., 2016 (n = 89) / Imai, H. et al., 2017 (n = 220) / Kim, K. M. et al., 2011 (n = 161)	Uramoto, H. et al. 2004 (n = 132)	Lee, H. Y. et al., 2019 (n = 31) /Wu, H. et al., 2014 (n = 40)
LYMPHOMA	-	Amengual, J. E. et al. 2016 (n = 82)	Chang, K. et al., 2010 (n = 156)
MYELOMA	Rasche, L. et al., 2016 (n = 50) / Adomako, A. et al., 2015 (n = 9)	-	Steiner, N. et al., 2017 (n = 73)
NEUROBLASTOMA	-	Weinreb, I. et al. 2009 (n = 20) / Hsu, W. et al., 2005 (n = 68)	-
ASTROCYTIC TUMORS	When, X. et al., 2020 (n = 28) / Ramão, A. et al., 2012 (n = 8) / Zhang, L. et al., 2011 (n = 115)	-	Peñaranda-Fajardo, N. M. et al., 2019 (n = 148)
MESOTHELIOMA	-	-	Dalton, L. E. et al. 2013 (n = 135)
ADVANCED THYMIC CARCINOMA	-	Miura, Y. et al. 2017 (n = 34)	-

TOTAL	61 studies n= 7905	10 studies n= 1064	20 studies n= 2134

APENDICE C- RELAÇÃO DE ESTUDOS SELECIONADOS EM RELAÇÃO À SOBREVIDA LIVRE DE DOENÇA, OU DE TE TEMPO PARA RECIDIVA E EXPRESSÃO DE GRP78

	HIGHEXPRESSION OF GRP78 and POOR DFS/RFS/PFS SURVIVAL	**HIGHEXPRESSION OF GRP78 and BETTER DFS/RFS SURVIVAL**	**NO STATISTICAL SIGNIFICANCE**
NASOPHARYNGEAL	Yi et al. (2015) n= 149 (DFS)	-	-
LARYNGEAL	-	Kaira et al. (2016) n =59 (PFS)	-
HYPOPHARYNGEAL	-	Kaira et al. (2016) n =68 l (PFS)	-
SALIVARY GLAND CANCER	Kaira et al. (2015) n =26 (PFS)	-	
LIVER	Feng et al. (2019) n=60 (PFS) after sorafenib tretament	-	Lee et al. (2013) n=190 (TTR)
COLORECTAL	Lee et al. (2015) n= 101 (RFS)		
MELANOMA	Shimizu et al. (2016) n=133 (PFS) Zhuang et al. (2009) n=141 (DFS)		
PROSTATE	Daneshmand et al. (2007) n=153 (RFS) Pootrakul et al. (2006) n= 219 (RFS)		
URINARY TRACT TUMORS		Uematsu et al. (2009) n=126 (DFS)	
BREAST	Yang et al. (2020) n=179 (DFS) Zheng et al. (2014) n= 213 (DFS) Tang et al. (2018) n= 121 (DFS)	Yerushalmi et al. (2015) n=19 CGRP78 (DFS)	Baptista et al. (2011) n=106 (DFS) Lee et al. (2006) n=127 (RRF) Lee et al. (2011) n=48 (RRF)
LUNG	Imai et al. (2017) n=118 stage I Lung AC (PFS) Kwon et al. (2018) n= 369 (DFS)	Imai et al. (2019) n= 105 *Patients with AC Component (DFS)	Lee et al. (2019) n=31 NSCLG (RFS)
ASTROCYTIC TUMORS	Zhang et al. (2011) n= 31 GBM PFS		
TOTAL	14 studies n= 2013	5 studies n= 377	5 studies n= 502

PFS, progression-free survival ; DFS, Disease-free survival; RFS, recurrence-free survival; TTR, time-to-recurrence survival; RRF, remaining-recurrence free; AC, adenocarcinoma

APÊNDICE D- RELAÇÃO DE ESTUDOS SELECIONADOS EM RELAÇÃO AO TRATAMENTO E EXPRESSÃO DE GRP78

	HIGHEXPRESSION OF GRP78 and POOR RESPONSE TO TREATMENT	HIGHEXPRESSION OF GRP78 and BETTER RESPONSE TO TREATMENT	NO STATISTICAL SIGNIFICANCE
NASOPHARYNGEAL	Feng et al. 92018) n=92 radioresistance Yi et al. (2015) n= 149 radioresistance		
ESOPHAGEAL		Slotta-Huspenina et al. (2013) n= 90 5-FU CTX	
GASTRIC	Yang et al. (2014) n=84 no-taxane CTX	Yang et al. (2014) n=76 taxane CTX	
COLORECTAL	Lee et al. (2015) n=101 5-FU ou leucoverin CTX Mhaidat et al. (2015) n=68 FOLFOX, FOLFORI, apcitabin with oxaplatin or bevacizumab regimen CTX	Thornton et al. (2013) n= 396 5-FU CTX	
PROSTATE	Tan et al. (2011) n= 164 castration CTX resistance Pootrakul et al. (2006) n= 219 castration CTX resistance		
BREAST	Zheng et al. (2014) n= 213 anthracycline-based CTX Lee et al. (2006) n= 102 *specific for patients receiveng doxorubicin and no taxane	Lee et al. (2011) n=48 doxorubicin and taxane combined CTX	Yerushalmi et al. (2015) n=19 CGRP78 CTX not specified Baptista et al. (2011) n=106 anthracycline-based CTX

ADVANCED THYMIC CARCINOMA			Miura et al. (2017) n=34 taxanes, topo II inhibitors CTX
TOTAL	9 studies n= 1192	4 studies n= 610	3 studies n= 159

APENDICE E – RELAÇÃO DE ESTUDOS SELECIONADOS EM RELAÇÃO A PRESENÇA DE METÁSTASES E EXPRESSÃO DE GRP78

	HIGHEXPRESSION OF GRP78 and more metastasis	HIGHEXPRESSION OF GRP78 and less metastasis	NO STATISTICAL SIGNIFICANCE
ORAL	Xia et al. (2014) n = 46	-	Kaira et al.(2016) n = 68
NASOPHARYNGEAL	Yi et al. (2015) n=149		
LARYNGEAL			Kaira et al.(2016) n= 59
ESOPHAGEAL	Ren et al. (2017) n= 92		
GASTRIC	Yang et al. (2014) n =237 Ogawa et al. (2017) n=328 Zheng et al. (2007) n =596	-	
PANCREAS	Klieser et al. (2015) n=49		
LIVER	Luo et al. (2018) n =112		Lee et al. (2013) n =190 Al-Rawashdeh et al. (2010) n=86 Luk et al. (2006) n= 67
COLORECTAL	Zhang, et al. (2012) n=198		
MELANOMA	Shimizu et al. (2016) n = 133		
BREAST	Yang et al. (2020) n = 179 Tang et al. 2018 n=121 Chen et al. (2014) n = 108 Bartkowiak et al. (2015) n = 89		
URINARY TRACT TUMOR	Wang et al. (2017) n=86		
OVARIAN			Huang et al. (2012) n = 96

ENDOMETRIAL	Guo et al.(2018) n=130		
LUNG	Yu et al. (2016) n = 89 Imai et al. 2019 n=105		Wang et al. (2020) n= 360 Lee et al. (2019) n=31 Kim et al. (2011) n = 152 Wu et al. (2014) n = 40 Imai et al. (2017) n = 150 Uramoto et al., (2004) n = 132 Kwon et al. (2018) n =369
TOTAL	18 studies n =2847		13 studies n = 1800