UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

DISSERTAÇÃO DE MESTRADO

Fatores Preditores para o Desenvolvimento de Pneumonia Hospitalar não Associada à Ventilação Mecânica: Revisão Sistemática e Metanálise

Stephani Amanda Lukasewicz Ferreira

Orientador: Profª. Dra. Patrícia Klarmann Ziegelmann

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Porto Alegre, março de 2018.

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MENSAGEM

"*The very first requirement in a hospital is that it should do the sick no harm*."

Florence Nightingale

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SUMÁRIO

ABREVIATURAS E SIGLAS

ANVISA	Agência Nacional de Vigilância Sanitária
ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
CPIS	Clinical Pulmonary Infection Score
EUA	Estados Unidos da América
HIV	Vírus da Imunodeficiência Humana
IHI	Institute for Healthcare Improvement
IRAS	Infecção Relacionada à Assistência à Saúde
NHSN	National Healthcare Safety Network
NNIS	National Nosocomial Infections Surveillance
OMS	Organização Mundial de Saúde
PAVM	Pneumonia Associada à Ventilação Mecânica
PNVM	Pneumonia não Associada à Ventilação Mecânica
SHEA	Society for Healthcare Epidemiology of America
UFC	Unidade Formadora de Colônia
UTI	Unidade de Terapia Intensiva
VM	Ventilação Mecânica

RESUMO

Introdução: A pneumonia hospitalar não associada à ventilação mecânica (PNVM) é uma infecção importante associada a alta morbidade e mortalidade e que, por ser distinta da pneumonia que se desenvolve em pacientes em ventilação mecânica, precisa ter seus fatores preditores estabelecidos. **Objetivo:** Identificar, quantificar e sumarizar a evidência existente na literatura sobre os fatores preditores para PNVM em pacientes adultos admitidos em unidades de cuidados não intensivos. **Métodos:** Uma busca sistemática da literatura foi realizada no PubMed, Embase, Scopus e LILACS. Estudos caso-controle e de coorte avaliando os fatores de risco para PNVM em pacientes adultos foram selecionados de acordo com os critérios de inclusão pré-definidos. Metanálise foi realizada para os fatores de risco para os quais os dados estavam disponíveis em mais de um estudo. A ferramenta de avaliação do *National Institute of Health* para estudos de coorte e caso-controle foi aplicada para avaliar a qualidade metodológica dos estudos incluídos. Foi atribuída uma avaliação com classificação de qualidade boa, razoável ou ruim para cada estudo. **Resultados:** Foram encontrados 11.380 estudos, 35 dos quais atendiam aos critérios de inclusão e fizeram parte desta revisão sistemática. A revisão encontrou 269 fatores de risco distintos, sendo que 58 estavam presentes em mais de um estudo e foram incluídos na metanálise com 33 significativamente associados à PNVM. A avaliação da qualidade foi realizada e 14 estudos foram classificados como ruins e 15 como qualidade razoável. A análise de sensibilidade foi realizada removendo os estudos classificados como ruins e 22 fatores de risco permaneceram significativamente associados à PNVM. **Conclusão:** A literatura mostra que existem 22 fatores de risco associados estatisticamente a PNVM. Mais estudos são necessários para estabelecer a associação dos fatores que não puderam ser associados a PNVM devido à baixa classificação da qualidade epidemiológica.

Palavras-chave: controle de infecção; pneumonia hospitalar; fatores de risco; revisão sistemática.

ABSTRACT

Background: Non-ventilated hospital acquired pneumonia (NVHAP) is an important infection associated to a high morbidity and mortality and, because it is distinct from pneumonia developing in patients undergoing mechanical ventilation, it must have its predictor factor established. **Aim:** To identify, quantify and summarize the existing evidence in the literature on the predictor factors for NVHAP in adult patients admitted to non-intensive care units. **Methods:** A systematic literature search was undertaken on PubMed, Embase, Scopus and LILACS. Case-control and cohort studies evaluating NVHAP predictor factors in adult patients were selected according to the inclusion criteria previously defined. Metanalysis was performed for those risk factors available from more than one study. The National Institute of Health assessment tool for cohort and case-control studies was applied to assess the quality of the included studies. An assessment of good, fair or poor quality rating was assigned for each study. **Findings:** A total of 11,380 studies were found, 35 of which met our inclusion criteria for this systematic review. The review found 269 distinct risk factors, of which 58 were present in more than one study and were included in the metanalysis with 33 being significantly associated to NVHAP. Quality assessment was performed and 14 studies were rated as poor and 15 as fair quality. Sensitivity analysis was performed without studies rated as poor in quality assessment and 22 risk factors remained significantly associated to NVHAP. **Conclusion:** Literature shows that there are 22 risk factors statistically associated to NVHAP. More studies are needed to establish the association of those factors that could not be associated to NVHAP due to poor quality rating.

Keywords: infection control; hospital-acquired pneumonia; risk factors; systematic review.

1 APRESENTAÇÃO

Este trabalho consiste na dissertação de mestrado intitulada “Fatores Preditores para o Desenvolvimento de Pneumonia Hospitalar não Associada à Ventilação Mecânica: revisão sistemática e metanálise”, apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul, em 28 de março de 2018. O trabalho é apresentado em três partes, na ordem que segue:

1. Introdução, Revisão da Literatura e Objetivos;
2. Artigo;
3. Conclusões e Considerações Finais.

Documentos de apoio estão apresentados nos anexos e apêndices.

2 INTRODUÇÃO

As infecções relacionadas à assistência à saúde (IRAS) são infecções que ocorrem durante o tratamento de condições médicas e cirúrgicas nas instituições de saúde e que não estavam presentes ou incubadas no momento da admissão. Atualmente, as IRAS são consideradas o evento adverso mais importante durante os cuidados de saúde que comprometem a segurança do paciente e que impactam em aumento do tempo de internação hospitalar, incapacidade a longo prazo, aumento da resistência dos microrganismos a agentes antimicrobianos, grandes encargos financeiros ao sistema de saúde, custos altos aos pacientes e suas famílias e mortes adicionais (World Health Organization, 2011).

A vigilância das IRAS é conceituada como "a coleta, análise e interpretação sistemática e contínua de dados de saúde essenciais ao planejamento, implementação e avaliação de práticas de saúde pública, intimamente integradas com a disseminação oportuna desses dados para aqueles que precisam saber" (Klaucke *et al*, 1988). A atividade de vigilância epidemiológica das IRAS é uma ferramenta essencial na redução da sua incidência uma vez que é a primeira etapa na identificação dos problemas para o estabelecimento de prioridades (Horan *et al*, 2008; World Health Organization, 2011).

Quando da realização da vigilância epidemiológica de infecções nas instituições de saúde é importante a distinção entre as definições de vigilância das IRAS e diagnóstico clínico. O diagnóstico clínico é baseado no julgamento, muitas vezes subjetivo, dos médicos e são utilizados para guiar o tratamento do paciente. Os critérios de vigilância são utilizados para se determinar de forma objetiva e padronizada a presença de uma infecção que é considerada relacionada aos cuidados de saúde para que se possa determinar as taxas de infecções das instituições e a necessidade de estabelecimento de medidas para prevenção e controle de tais complicações, assim como a comparabilidade dos dados entre instituições. As definições para vigilância das IRAS não têm o objetivo de realizar o diagnóstico clínico ou de guiar o tratamento do paciente (Agência Nacional de Vigilância Sanitária, 2017; Horan *et al*, 2008; Talbot *et al*, 2013).

Nas últimas décadas, dados de vigilância epidemiológica vêm demonstrando que as IRAS representam um grande problema nas instituições de saúde em todo o mundo, com cerca de 5 a 10% do total de admissões hospitalares complicadas por infecções (Research Committee of the Society of Healthcare Epidemiology of America, 2010). Dados europeus estimam que as IRAS causem 16 milhões de dias adicionais de internação hospitalar, 37.000 mortes atribuídas e um custo direto de sete bilhões de euros por ano (World Health

Organization, 2011). Dados similares foram reportados nos Estados Unidos da América (EUA) onde em 2002 cerca de duas milhões de pessoas desenvolveram pelo menos uma infecção hospitalar e aproximadamente 100.000 mortes foram atribuídas a IRAS, sendo 36.000 devido as pneumonias, 31.000 as infecções primárias de corrente sanguínea, 13.000 as infecções do trato urinário e 8.200 as infecções de sítio cirúrgico (Klevens *et al*, 2007). Nos EUA o impacto econômico das IRAS chega a aproximadamente US$20 bilhões em um ano (Research Committee of the Society of Healthcare Epidemiology of America, 2010). Uma pesquisa que teve como objetivo estimar a prevalência de IRAS nos hospitais americanos encontrou um dado alarmante de que 1 em cada 25 pacientes possuíam uma infecção adquirida nas instituições de saúde, resultando em uma estimativa de 648.000 pacientes com um total de 721.800 infecções em um ano (Magill *et al*, 2014).

Em países em desenvolvimento os dados sobre IRAS são muito escassos. Comparado a prevalência média de IRAS na Europa, que é de 7%, e nos EUA, de 4,5%, a prevalência nos países em desenvolvimento é substancialmente alta, chegando a 15,5%, com um excesso de mortalidade que pode chegar a 30%. No Brasil, uma revisão sistemática realizada pela Organização Mundial de Saúde (OMS) identificou uma prevalência de 14% de IRAS no Brasil (Allegranzi *et al*, 2011; World Health Organization, 2011).

As IRAS relacionadas aos dispositivos invasivos, tais como ventilação mecânica (VM), cateter venoso central e cateter urinário, que vem sendo o maior foco da realização de estudos nas últimas décadas, têm se mostrado menos importantes em pesquisas recentes. Estudo americano desenvolvido em 183 hospitais que incluiu 11.282 pacientes encontrou um total de 504 infecções em 452 pacientes. Esta pesquisa mostrou que as infecções relacionadas aos dispositivos invasivos contribuíram para apenas 25,6% do total de IRAS e que quando somadas às infecções de sítio cirúrgico totalizaram 47,4%. Já as infecções restantes (52,6%) foram atribuídas àquelas não relacionadas aos dispositivos invasivos, incluindo as pneumonias hospitalares não associadas à ventilação mecânica (PNVM) (Magill *et al*, 2014).

As pneumonias hospitalares, sejam associadas ou não à ventilação mecânica (VM), estão entre as IRAS mais prevalentes nas instituições de saúde. Nos EUA, onde estes dados estão mais facilmente disponíveis, é estimado que as pneumonias hospitalares sejam responsáveis por 15 a 20% do total de infecções adquiridas nos hospitais (Magill *et al*, 2014; Research Committee of the Society of Healthcare Epidemiology of America, 2010). O *Centers for Disease Control and Prevention* (CDC) estima que mais de dois terços das, aproximadamente, 157.000 pneumonias adquiridas nos hospitais todos os anos nos EUA ocorrem em pacientes que não utilizam VM (Klompas, 2016). Para o órgão americano, do

total das pneumonias hospitalares, 60-70% são não associadas à VM, sendo responsáveis por aproximadamente 20% da mortalidade hospitalar (Davis; Finley, 2012; Magill *et al*, 2014).

A densidade de incidência das PNVM é difícil de ser estabelecida, uma vez que a dispersão de casos entre as unidades dos hospitais, as falhas e dificuldades na vigilância, a possibilidade de apresentação após a alta hospitalar e a dificuldade na realização de técnicas invasivas para identificação dos agentes etiológicos tornam os dados existentes não comparáveis e muito distintos entre si. Alguns estudos mostram a taxa de incidência de pneumonia fora das unidades de terapia intensiva (UTI) entre 3,1 e 3,3 casos/1000 pacientes-dia (Edis *et al*, 2009; Sopena; Sabrià, 2005). Em um estudo realizado no Japão a incidência foi de 18,6 casos/1000 pacientes-dia em um hospital terciário. Estas diferenças podem ser explicadas pelos diferentes métodos utilizados na definição e identificação dos casos e as diferenças nas características da população em estudo (Ohi *et al*, 2004).

Estudos que compararam os desfechos de pacientes com PNVM com pacientes sem tal desfecho ou com pneumonias comunitárias, os primeiros foram estatisticamente mais prováveis a morrer durante a internação hospitalar, necessitar de internação em UTI e uso de VM. Ainda, o desenvolvimento da pneumonia está associado a aumento do tempo de internação hospitalar, onde os pacientes com pneumonia hospitalar permanecem internados em média 15,2 dias, podendo chegar a uma internação superior a 20 dias, em comparação a 4,4 dias dos pacientes sem pneumonia e 8,8 dias dos pacientes com pneumonia comunitária (Baker; Quinn, 2018; Kollef *et al*, 2005; Micek *et al*, 2016; Zhang; Duan, 2015).

Esta importante complicação infecciosa está associada ainda a aumento dos custos com a internação hospitalar. Estudo desenvolvido na Turquia que comparou os custos da internação hospitalar de pacientes com e sem pneumonia hospitalar mostrou que o custo do grupo com pneumonia foi significativamente maior que do grupo sem tal infecção, sendo o custo total do primeiro grupo de $6.240 e no grupo controle de $1.117. Esta análise exclui o custo com antibióticos para tratamento da pneumonia, o que adicionaria aos custos um total de $1.062 (Edis; Hatipoglu; Yilmam, 2015).

Estudo americano realizado em 59 hospitais também mostrou aumento dos custos hospitalares para o tratamento das pneumonias adquiridas nas instituições de saúde. Enquanto as pneumonias comunitárias custaram US$25.218 por episódio, as PNVM estiveram associadas a um custo total de US$65.292 (Kollef *et al*, 2005). Já um estudo desenvolvido na Pensilvânia e que estimou os custos com as pneumonias hospitalares em um período de três anos mostrou que o custo com as PNVM pode chegar a US$55.343 por episódio, enquanto que o custo com PAVM foi estimado em até $34.521 (Davis; Finley, 2012). A diferença nos

custos entre os dois países pode ser justificada pelo menor custo por leito hospitalar na Turquia, no entanto, ambos estudos demonstram a carga econômica que pode ser atribuída as instituições e ao sistema de saúde quando um paciente desenvolve uma pneumonia durante a sua internação hospitalar. Dessa forma, o entendimento dos fatores de risco para o desenvolvimento de estratégias para prevenção de tal complicação infecciosa é de fundamental relevância para a prática clínica.

3 REVISÃO DE LITERATURA

3.1 DEFINIÇÃO DE PNEUMONIA

A pneumonia hospitalar é definida pelo *American Thoracic Society* (ATS) como a infecção do trato respiratório inferior que se desenvolve a partir de 48 horas de hospitalização e que não estava presente ou incubada no momento da admissão hospitalar. As pneumonias hospitalares podem ser classificadas em pneumonias associadas à ventilação mecânica (PAVM) ou pneumonias não associadas à VM (PNVM) (American Thoracic Society, 2005; Masterton *et al*, 2008).

A pneumonia relacionada à assistência à saúde é um conceito de infecção do trato respiratório utilizado que abrange o tratamento hospitalar recente e a assistência prestada em instituições de longa permanência. Esta infecção afeta uma população diferente de pacientes quando comparadas com as pneumonias comunitárias que ocorrem em pacientes não hospitalizados e que preenchem um ou mais dos seguintes critérios: internação hospitalar por dois ou mais dias nos últimos 90 dias; residentes de instituições de longa permanência destinadas a portadores de doenças crônicas; pacientes que receberam terapia intravenosa, quimioterapia ou cuidados de feridas nos 30 dias antecedentes ao início da infecção; e ou atendimento hospitalar ou hemodialítico nos últimos 30 dias (American Thoracic Society, 2005).

A PAVM, subtipo das pneumonias adquiridas no hospital, é aquela que se desenvolve após 48 horas do início do uso da VM invasiva (American Thoracic Society, 2005; Masterton *et al*, 2008; Ottosen; Evans, 2014). A VM é o método de suporte ventilatório com pressão positiva que utiliza próteses introduzidas na via aérea, como o tubo orotraqueal ou a cânula de traqueostomia, para o tratamento de pacientes que necessitam de proteção das vias aéreas. A VM é indicada nos casos de depressão do nível de consciência (exemplo: traumas cranianos, acidente vascular encefálico), insuficiência respiratória devido a doenças respiratórias, musculares ou da parede torácica ou por insuficiência circulatória. O principal objetivo é a manutenção das trocas gasosas pela correção da hipoxemia e acidose respiratória associada à hipercapnia, alívio do trabalho da musculatura respiratória, diminuição do consumo de oxigênio e aplicação de terapêuticas específicas (Pham; Brochard; Slutsky, 2017).

Já as PNVM, objeto de estudo deste trabalho, ocorrem naqueles pacientes que estão internados em hospitais e não estão em uso de VM invasiva, independente se desenvolvidas

dentro da UTI ou em unidades de cuidados não intensivos (American Thoracic Society, 2005; Masterton *et al*, 2008). As PNVM são frequentemente classificadas em precoces e tardias. A pneumonia é considerada precoce quando ocorre dentro de 4-5 dias após a admissão hospitalar e tende a ser causada por microrganismos do tipo comunitário sensíveis aos antibióticos. Já as pneumonias tardias ocorrem após os cinco dias de admissão hospitalar e são geralmente causadas por microrganismos oportunistas de origem hospitalar (Masterton *et al*, 2008). Esta designação é baseada na premissa de que a flora bacteriana da orofaringe é modificada ao longo do tempo pelo ambiente de assistência à saúde (Ottosen; Evans, 2014).

3.2 ETIOLOGIA

As pneumonias hospitalares são causadas por um amplo espectro de patógenos originários do ambiente de cuidados de saúde ou ainda pela própria flora endógena dos pacientes. A etiologia das PNVM desenvolvidas fora da UTI se distingue daquelas associadas à VM, especialmente devido a menor agressão e menor mudança na flora da orofaringe. Assim como as pneumonias desenvolvidas em pacientes ventilados, as PNVM podem ser de etiologia polimicrobiana e raramente são causadas por patógenos virais ou fúngicos em pacientes imunocompetentes (American Thoracic Society, 2005; Nair; Niederman, 2013; Sabrià; Sopena, 2011).

A etiologia das PNVM é geralmente multifatorial, estando relacionada com o tipo de paciente atendido na instituição de saúde (pacientes clínicos ou cirúrgicos), a sua complexidade (comorbidades e gravidade), o tempo de internação prévio ao desenvolvimento da infecção, o estado de saúde do paciente antes do início da infecção, a história prévia de uso de antimicrobianos, o histórico de residência em instituições de longa permanência e, especialmente, as técnicas de diagnóstico utilizadas para a identificação da pneumonia (Sopena; Sabrià, 2005).

O período de desenvolvimento da pneumonia hospitalar é uma variável epidemiológica importante na caracterização da etiologia da mesma. Pneumonias hospitalares precoces usualmente possuem um melhor prognóstico e são mais comumente causadas por microrganismos sensíveis aos antimicrobianos. Estas pneumonias são geralmente causas por microrganismos de origem comunitária como *Streptococcus pneumoniae* e *Haemophilus influenzae*. No entanto, microrganismos gram-negativos não resistentes, como *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp, *Proteus* spp, *Serratia marcescens* e *Pseudomonas aeruginosa*, assim como *Staphylococcus aureus* sensível a meticilina também podem estar

presentes nas pneumonias de origem precoce (American Thoracic Society, 2005; Jones, 2010; Kollef *et al*, 2005; Lynch, 2001; Mastertorn *et al*, 2008; Nair; Niederman, 2013; Russell *et al*, 2016; Sabrià; Sopena, 2011; Seligman *et al*, 2013; Sopena, 2005a; Torres *et al*, 2009).

As pneumonias hospitalares de origem tardia, que se desenvolvem após 5 dias de internação, são geralmente causadas por bacilos gram-negativos aeróbios, como *P. aeruginosa*, Enterobactérias, *Acinetobacter* spp e *S. aureus*, sendo responsáveis por até 70% dos casos de pneumonias tardias. Nestas pneumonias, os microrganismos responsáveis são mais frequentemente resistentes aos antimicrobianos comumente utilizados no tratamento, como os carbapenêmicos e meticilina (American Thoracic Society, 2005; Jones, 2010; Kollef *et al*, 2005; Lynch, 2001; Mastertorn *et al*, 2008; Nair; Niederman, 2013; Russell *et al*, 2016; Seligman *et al*, 2013; Sopena, 2005a; Torres *et al*, 2009).

Microrganismos como *Acinetobacter* spp, *P. aeruginosa* e outros bacilos gram-negativos resistentes, incluindo as enterobactérias produtoras de beta lactamase de espectro ampliado ou de carbapenemases são menos frequentes na etiologia das PNVM desenvolvidas em unidades de cuidados não intensivos comparativamente à UTI onde há uma maior exposição e maior prevalência de colonização por estes microrganismos. Fatores que influenciam no desenvolvimento de PNVM causadas por microrganismos resistentes como *S. aureus* resistente a meticilina, *P. aeruginosa* e *Acinetobacter* spp resistentes a carbapenêmicos incluem: uso de terapia antimicrobiana e hospitalização nos últimos 90 dias; residir em instituições de longa permanência; necessidade de cuidados crônicos fora da instituição hospitalar (como hemodiálise); hospitalização atual com duração superior a cinco dias; alta frequência de microrganismos resistentes na instituição; doença ou terapia imunossupressora; e doença de base severa (como as doenças pulmonares) (American Thoracic Society, 2005; Nair; Niederman, 2013; Sabriá; Sopena, 2011; Seligman *et al*, 2013; Sopena 2005a).

Infecções causadas por fungos e patógenos raros como *Aspergillus* spp, *Pneumocystis jiroveci*, *Candida* spp, *Nocardia* spp e vírus como *Cytomegalovirus* devem ser suspeitados em pacientes imunossuprimidos (Nair; Niederman, 2013). A imunossupressão inclui os pacientes com neutropenia (contagem absoluta de neutrófilos <500/mm^3); leucemia; linfoma; presença de infecção pelo vírus da imunodeficiência humana (HIV) com contagem de CD4 <200; esplenectomia; transplantados; uso de quimioterapia citotóxica; ou com uso de altas doses de corticoides ou outros imunodepressores diariamente por > 2 semanas (como >40mg de prednisona ou seu equivalente, >160mg de hidrocortisona, >32mg de metilprednisolona, >6mg dexametasona, >200mg cortisona) (Agência Nacional de Vigilância Sanitária, 2017).

3.3 PATOGÊNESE DAS PNEUMONIAS RELACIONADAS À ASSISTÊNCIA À SAÚDE

O desenvolvimento da PNVM pode estar relacionado a diferentes mecanismos. A interação entre as defesas do hospedeiro e a habilidade dos microrganismos em colonizar e invadir o trato respiratório inferior determina se o paciente irá ou não desenvolver a infecção. (American Thoracic Society, 2005; Sabriá; Sopena, 2011).

O principal mecanismo considerado como fator desencadeante da PNVM é a microaspiração de secreções do trato respiratório superior para o trato respiratório inferior, condição presente em até 45% dos adultos saudáveis durante o sono (American Thoracic Society, 2005; Tablan *et al*, 2004). Em pacientes não submetidos à VM invasiva, as microaspirações podem ocorrer espontaneamente, sendo relacionadas a fatores como diminuição do nível de consciência, desordens de deglutição e alterações no reflexo da tosse e motilidade gastrointestinal (Sabrià; Sopena, 2011; Sopena, 2005a; Tablan *et al*, 2004). A inoculação de uma grande quantidade de patógenos virulentos, como nas situações em que há aspirações maciças, pode resultar em pneumonia, uma vez que as defesas do paciente não podem conter adequada e rapidamente a infecção (Nair; Niederman, 2013).

A alta incidência de pneumonias adquiridas no hospital por bacilos gram-negativos é o resultado da colonização da orofaringe que ocorre por estes microrganismos e que posteriormente entram no trato respiratório inferior a partir das microaspirações das secreções do trato respiratório superior (Tablan *et al*, 2004). Na comunidade, a flora da orofaringe é constituída basicamente por microrganismos gram-positivos. Já em pacientes hospitalizados a flora da orofaringe pode mudar para a predominância de bacilos gram-negativos em 35-75% dos pacientes nos primeiros cinco dias após a admissão. Esta mudança dependerá da severidade e tipo de doença de base do paciente, da presença de comorbidades e de fatores como desnutrição, uso de antimicrobianos, realização de procedimentos cirúrgicos e admissão prévia em unidade de terapia intensiva (American Thoracic Society, 2005; Nair; Niederman, 2013; Niederman, 2010; Sabrià, Sopena, 2011).

Além da orofaringe, o estômago tem sido considerado um reservatório de organismos relacionados à ocorrência de PNVM. O papel que o estômago desempenha pode variar dependendo das condições de base do paciente e da intervenção terapêutica profilática que o mesmo recebe. Em pessoas saudáveis, poucas bactérias que entram no estômago sobrevivem, uma vez que a presença do ácido clorídrico torna este um ambiente inóspito aos microrganismos. Entretanto, quando o pH gástrico aumenta dos níveis normais ($pH < 2$) para níveis superiores ($pH > 4$), os microrganismos são capazes de sobreviver e se multiplicar em

altas concentrações. Esta condição ocorre em pacientes com idade avançada, acloridria, doenças do trato gastrointestinal superior, indivíduos recebendo nutrição enteral, antiácidos ou antagonistas de receptores da histamina$_2$ (Tablan *et al*, 2004). A microaspiração direta de conteúdos gástricos para as vias aéreas inferiores, particularmente quando o paciente está na posição supina, pode favorecer o desenvolvimento de pneumonias. O uso de medicação supressora do ácido gástrico, como inibidores da bomba de próton e antagonistas dos receptores de histamina$_2$, utilizados como profilaxia de úlcera de estresse, modifica a flora gastrointestinal, e como resultado a flora respiratória, através da redução do pH gástrico predispondo os pacientes ao risco de pneumonias (Herzig *et al*, 2009).

A inalação de aerossóis aquosos, provenientes de chuveiros e torneiras, ou aéreos, da poeira ou partículas de saliva, tem sido relacionado a pneumonia por *Legionella* spp, *Aspergillus* spp, *Chlamydophila pneumonia* e vírus em pacientes que não estão recebendo VM invasiva (Sabrià; Sopena, 2011; American Thoracic Society, 2005).

Outros mecanismos considerados importantes na patogênese das pneumonias nosocomiais incluem a aspiração de bactérias de placas dentárias e a inalação de aerossóis de dispositivos de assistência ventilatória contaminados, como nebulizadores e umidificadores que não receberam o adequado processamento (desinfecção de alto nível ou esterilização) dentro da instituição de saúde (American Thoracic Society, 2005). A pneumonia nosocomial originada pela disseminação hematogênica de uma infecção de outro sítio para o pulmão é rara (Tablan *et al*, 2004).

3.4 DIAGNÓSTICO DAS PNEUMONIAS NÃO RELACIONADAS À VENTILAÇÃO MECÂNICA

O diagnóstico da pneumonia, seja relacionada ou não à VM, é difícil, e não há uma definição que seja aceita universalmente, dada sua subjetividade e baixa especificidade. A subjetividade na definição da pneumonia está nas diferenças entre observadores quanto à identificação dos sinais e sintomas clínicos e na variabilidade da interpretação dos achados radiológicos. O diagnóstico da pneumonia hospitalar é difícil, variável e propenso a erros, especialmente em pacientes com comorbidades cardiopulmonares de base (American Thoracic Society, 2005; Klompas *et al*, 2014).

A definição para pneumonia descrita em diretrizes de especialidades médicas é a mesma tanto para as pneumonias hospitalares, PNVM e PAVM, como para as pneumonias

relacionadas à assistência à saúde e pneumonias comunitárias. A presença de um infiltrado pulmonar novo ou progressivo na radiografia de tórax, acompanhado de pelo menos dois dos três achados clínicos que sugiram a infecção, tais como febre (temperatura corporal acima de 38ºC), leucocitose (>12.000 leucócitos/mm^3) ou leucopenia (<4.000 leucócitos/mm^3) e a ocorrência de secreção respiratória purulenta constituem a combinação de critérios considerada como a mais acurada no diagnóstico da pneumonia (American Thoracic Society, 2005; Dalhoff; Ewig, 2013; Masterton *et al*, 2008).

O *Clinical Pulmonary Infection Score* (CPIS) é um escore clínico que foi desenvolvido com o objetivo de diagnosticar as pneumonias adquiridas no hospital. Este escore utiliza seis critérios para a definição da pneumonia: febre, secreção respiratória purulenta, leucocitose, piora na oxigenação, grau de alteração na radiografia de tórax e a cultura semi-quantitativa de secreção respiratória. Cada item é pontuado em uma escala de 0 a 2, sendo que um escore igual ou maior a 6 é indicativo da presença da infecção pulmonar (Pugin *et al*, 1991). Embora este critério não tenha demonstrado aumentar a acurácia no diagnóstico da pneumonia quando comparado ao critério clínico convencional, o mesmo tem sido utilizado para embasar decisões de monitoramento, modificações e ajustes na terapia antimicrobiana em curso (Mastertorn *et al*, 2008).

O diagnóstico microbiológico, sempre que possível, auxilia na adequação do tratamento antimicrobiano e melhora o prognóstico dos pacientes por direcionar o tratamento para o microrganismo correto levando em consideração o seu perfil de sensibilidade, reduzindo assim, o tempo de terapia antimicrobiana e de internação hospitalar. Culturas quantitativas devem ser obtidas a partir de amostras do trato respiratório inferior, como através dos exames realizados mediante escovado protegido e lavado broncoalveolar, antes do início da terapia antimicrobiana (American Thoracic Society, 2005). No entanto, estas técnicas invasivas são menos indicadas para o diagnóstico da pneumonia em pacientes que não estão recebendo VM invasiva, uma vez que podem desencadear complicações como hipoxemia, sangramentos e arritmias. A estratégia diagnóstica realizada a partir de endoscopia respiratória é indicada para pacientes em VM, indivíduos apresentando imunossupressão e aqueles que não apresentam melhora clínica após 48 a 72 horas do início do tratamento antimicrobiano empírico ou direcionado por resultados de exames microbiológicos e tem o objetivo de reduzir a contaminação das amostras respiratórias com microrganismos que colonizam o trato respiratório superior do paciente (Sopena, 2005a; Tablan *et al*, 2004).

Para pacientes que não estão recebendo VM não se recomenda o uso de procedimentos invasivos para o diagnóstico da pneumonia, visando evitar a exposição do paciente a

procedimentos de risco e pelo alto custo diretamente associado a eles. Para o diagnóstico microbiológico de PNVM devem ser coletadas amostras de escarro para avaliação da coloração de Gram e cultura microbiológica quantitativa. No entanto, em muitos casos, estas amostras são difíceis de serem obtidas, além de possuir valor diagnóstico limitado devido as chances de contaminação das amostras pela flora da orofaringe. Ainda, o atraso no processamento destas amostras pode favorecer o crescimento de bacilos gram-negativos e *Staphylococcus* spp e minimizar a presença de outros microrganismos importantes como *S. pneumoniae* e *H. influenzae* e que podem ser os reais causadores do processo infeccioso. Para pacientes com depressão do nível de consciência ou portadores de traqueostomia pode ser útil a coleta de aspirado traqueal, porém estas amostras possuem as mesmas limitações das amostras de escarro em relação a acurácia e risco de contaminação com a flora do trato respiratório superior. A coloração de Gram fornece informações da qualidade da amostra respiratória coletada. Amostras de escarro consideradas como representativas do trato respiratório inferior deverão possuir mais de 25 leucócitos e menos de 10 células escamosas por campo (Sabrià; Sopena, 2011; Sopena 2005a). Na maior parte dos casos, é possível se realizar o diagnóstico da pneumonia quando a cultura aponta a presença de um patógeno que não faz parte da flora comensal oral (Dalhoff; Ewig, 2013; Ottosen; Evans, 2014; Sopena 2005a).

Geralmente a confirmação microbiológica é baseada nas culturas quantitativas com contagem bacteriana acima do limiar diagnóstico de $1x10^3$ unidades formadoras de colônia (UFC)/mL em escovado protegido, $1x10^4$ UFC/mL ou $1x10^5$ UFC/mL para amostras de lavado broncoalveolar e $1x10^6$ UFC/mL em amostras de aspirado traqueal e escarro. No entanto, na prática clínica, frequentemente pode ser difícil a coleta de amostras respiratórias para cultura quantitativa antes do início da administração do antimicrobiano, o que pode reduzir a contagem quantitativa de bactérias nestas amostras (Niederman, 2010).

O uso do critério microbiológico na definição das PNVM auxilia na escolha da terapêutica antimicrobiana empírica mais adequada ao paciente, reduzindo o risco de mortalidade, o potencial uso de antimicrobianos tóxicos, além de reduzir as chances de seleção de microrganismos resistentes ou o tratamento de causas não-infecciosas de febre e infiltrados pulmonares (Di Pasquale *et al*, 2016).

3.4.1 Critérios para definição epidemiológica de pneumonia não relacionada à ventilação mecânica

Para a definição dos casos de pneumonias hospitalares a serem identificados pelas comissões de controle de infecção nas suas atividades de vigilância epidemiológica, existem critérios definidos por entidades nacionais e internacionais de especialistas que devem ser utilizados. Esta vigilância, através de critérios previamente definidos, visa a identificação padronizada das pneumonias hospitalares permitindo o estabelecimento de indicadores institucionais de infecção do trato respiratório e a comparabilidade entre instituições de saúde com perfil de pacientes similar tanto a nível nacional quanto internacional. Os três principais componentes para detecção das PNVM são: radiografia de tórax, sinais e sintomas clínicos e exames laboratoriais. É importante ressaltar que apenas o diagnóstico clínico do médico para a pneumonia não é suficiente para a definição epidemiológica de PNVM (Centers for Diasease Control and Prevention, 2018).

A definição de PNVM utilizada pelo *National Healthcare Safety Network* (NHSN) do CDC é similar àquela utilizada para a pneumonia definida mediante critérios clínicos. No entanto, para que seja caracterizada como uma infecção adquirida no hospital o paciente deve preencher rigorosamente aos critérios estabelecidos pela entidade. No Brasil, a Agência Nacional de Vigilância Sanitária (ANVISA), órgão regulatório para uso de medicamentos e demais equipamentos e tecnologias em saúde, definiu os critérios nacionais para as IRAS utilizando os mesmos critérios do CDC/NHSN (Agência Nacional de Vigilância Sanitária, 2017). Os critérios utilizados para a definição de PNVM estão descritos no Quadro 1.

Quadro 1 – Critérios para Definição Clínica e Microbiológica de Pneumonia não Relacionada à Ventilação Mecânica

Pneumonia não Associada à Ventilação Mecânica definida Clinicamente	**Dois** ou mais exames de imagem torácica com pelo menos uma das alterações: • Infiltrado; • Consolidação; • Cavitação. **Pelo menos uma** das seguintes alterações: • Febre (>38ºC); • Leucopenia (<4.000 leucócitos/mm^3) ou leucocitose (>12.000

	leucócitos/mm^3); • Em adultos com mais de 70 anos, estado mental alterado sem outra causa reconhecida. E pelo menos a presença de **duas** das seguintes alterações clínicas: • Início de escarro purulento ou mudança na característica do escarro ou aumento no volume de secreção respiratória ou aumento na necessidade de aspirações; • Início ou piora da tosse ou dispneia ou taquipneia; • Respiração brônquica ou sibilos; • Piora das trocas gasosas (dessaturações, relação $PaO_2/FiO_2 < 240$), aumento da necessidade de oxigênio ou aumento na demanda ventilatória.
Pneumonia não Associada à Ventilação Mecânica definida Microbiologicamente	Todos os critérios para pneumonia definida clinicamente somados aos critérios abaixo. Pelo menos **um** dos seguintes achados: • Hemocultura positiva que não esteja associada a infecção em outro sítio; • Cultura positiva de fluido pleural; • Cultura quantitativa de lavado broncoalveolar ou escovado protegido positivos; • Bacterioscopia do lavado broncoalveolar com presença de bactérias intracelulares em exame microscópico direto; • Cultura positiva quantitativa de tecido pulmonar; • Exame histopatológico com pelo menos uma das seguintes evidências: o Formação de abscesso ou foco de consolidação com intenso acúmulo de polimorfonucleares nos bronquíolos e alvéolos; o Evidência de invasão do parênquima pulmonar por hifas fungicas ou pseudohifas. • Vírus, *Bordetella*, *Legionella*, *Chlamydophila* ou *Mycoplasma* identificados a partir de cultura de secreção ou tecido pulmonar identificados por teste microbiológico realizado para fins de diagnóstico clínico ou tratamento; • Aumento de quatro vezes nos valores de IgG na sorologia para

	patógeno (exemplo: influenza, *Chlamydophila*); • Aumento de quatro vezes nos valores de IgG na sorologia para *Legionella pneumophila* sorogrupo I titulada >1:128 na fase aguda por imunofluorescência indireta; • Detecção de antígeno de *Legionella pneumophila* sorogrupo I em urina.

Fonte: Centers for Disease Control and Prevention. Pneumonia (ventilator-associated [VAP] and non-ventilator-associated Pneumonia [PNEU]) Event. 2018a. Agência Nacional de Vigilância Sanitária. Critérios Diagnósticos de Infecção Relacionada à Assistência à Saúde. Brasília:Anvisa, 2017.

3.5 VIGILÂNCIA DAS INFECÇÕES RELACIONADAS À ASSISTÊNCIA À SAÚDE E CRITÉRIOS DE DEFINIÇÃO

A vigilância epidemiológica das IRAS é reconhecida como pilar dos programas de prevenção e controle de infecção desenvolvida em instituição de saúde. Esta vigilância é realizada por um profissional de controle de infecção treinado que busca as infecções que foram adquiridas durante a internação do paciente com o objetivo de estabelecer as taxas de infecção da instituição (Talbot *et al*, 2013). A busca dos dados ocorre através de uma grande variedade de fontes, tais como resultados de exames laboratoriais (como leucograma e proteína C reativa), histórico do uso de antimicrobianos, resultados de exames radiológicos e de imagem (como tomografias computadorizadas, raio-X e ecografias), informações sobre admissões/altas/transferências e outros dados disponíveis nos prontuários dos pacientes registrados pela equipe assistencial bem como a evolução clínica do paciente (Centers for Disease Control and Prevention, 2018). A busca baseada em dados microbiológicos é uma forma de vigilância epidemiológica, mas que não deve ser utilizada isoladamente, a não ser que o critério para identificação da infecção seja apenas determinado quando a evidência microbiológica está presente (Centers for Disease Control and Prevention, 2018).

A vigilância epidemiológica deve ser conduzida por profissionais de controle de infecção capacitados que aplicam técnicas de definições complexas na população estudada. As primeiras definições para as IRAS foram desenvolvidas em 1970 pelo *National Nosocomial Infections Surveillance* (NNIS) do CDC com o objetivo de classificar internamente as métricas de qualidade das instituições norte-americanas para guiar ações locais de prevenção e controle de infecção. Através deste sistema, as instituições poderiam realizar práticas de *benchmark* de seu desempenho interno quanto à ocorrência das IRAS

comparando a um grupo de hospitais do país que também relatam os seus dados ao sistema nacional (Talbot *et al*, 2013).

No Brasil, a Portaria GM/MS nº 2616/98 determina a obrigatoriedade dos serviços de saúde em coletar as informações relativas aos indicadores de infecção (Brasil, 1998). Os primeiros critérios para definição de IRAS foram desenvolvidos em 2010 pela ANVISA e a disponibilização de um formulário eletrônico para inserção dos dados das instituições hospitalares brasileiras ocorreu neste mesmo ano (Brasil, 2018). Até o final de 2016, era obrigatória a notificação a nível nacional apenas das infecções primárias de corrente sanguínea, sendo possível realizar o *benchmark* nacional apenas desta topografia de infecção. Em 2017, com a publicação do Programa Nacional de Prevenção e Controle das IRAS 2016-2020, houve a ampliação do número de indicadores nacionais de notificação obrigatória, sendo agora necessária a notificação das PAVM e infecções do trato urinário relacionadas ao uso de sondagem vesical de demora no sistema nacional brasileiro (Brasil, 2016; Brasil, 2018).

A vigilância epidemiológica das IRAS pode ser realizada de duas maneiras: global ou específica. A vigilância global consiste na busca ativa e sistemática de todas as infecções que ocorrem na instituição de saúde. No entanto, com o aumento da complexidade dos cuidados aos pacientes e, subsequente aumento na carga de trabalho necessária à coleta dos dados, a vigilância passou a ser realizada de forma mais específica focada em infecções que ocorrem em unidades críticas, como UTI, e que são relacionadas aos dispositivos invasivos, como a PAVM, ou procedimentos de maior risco, como as cirurgias (Talbot *et al*, 2013). Dessa forma, as pneumonias que ocorrem em pacientes não submetidos à VM, especialmente nas unidades não críticas, acabam não sendo identificadas e contabilizadas.

Embora, as definições de IRAS promovam um processo padronizado para determinação da ocorrência das infecções nas instituições de saúde, o uso dos critérios também está associado a variações de interpretação. Alguns componentes das definições de caso são subjetivos, como a presença de secreção traqueal purulenta para determinar a ocorrência de uma pneumonia. Ainda, para determinar a ocorrência de IRAS torna-se necessária a documentação de dados clínicos do paciente por parte da equipe assistencial e da variabilidade da interpretação dos achados entre os membros da equipe quando da avaliação do paciente. O acesso aos dados também pode ser uma dificuldade na definição dos critérios de infecção, uma vez que muitas fontes de dados são necessárias para se aplicar as definições de caso e a dificuldade no acesso a estas informações pode prejudicar a classificação final da infecção (Talbot *et al*, 2013).

Para as definições de PNVM a vigilância epidemiológica torna-se ainda mais difícil e trabalhosa, contribuindo para a redução da confiabilidade da definição das taxas de infecção. Primeiro, porque a definição do caso de PNVM depende de muitos fatores clínicos, como piora respiratória e alterações nas características da secreção respiratória, e existem poucos critérios laboratoriais, característica mais específica para o diagnóstico, que possam auxiliar na seleção dos pacientes, exigindo assim uma avaliação completa dos dados dos pacientes para a definição dos casos. Segundo, porque devido às dificuldades de realização de vigilância global, a maior parte das instituições opta pela realização da vigilância epidemiológica das infecções relacionadas aos dispositivos invasivos, baseada apenas nas culturas microbiológicas (dessa forma PNVM definidas apenas clinicamente ficam de fora da vigilância) ou apenas aquelas identificadas nas UTI, o que acaba por excluir as PNVM que ocorrem em unidades de internação, deixando esta importante topografia sem dados epidemiológicos consistentes que possam estimular a implantação de medidas de prevenção e controle (Klompas, 2016).

3.6 PREVENÇÃO DAS PNEUMONIAS RELACIONADAS À ASSISTÊNCIA À SAÚDE

Diversas estratégias preventivas vêm sendo desenvolvidas para reduzir a incidência das pneumonias hospitalares. O conhecimento dos fatores implicados no desenvolvimento destas pneumonias permite o desenvolvimento de estratégias que visem a prevenção desta complicação (Sabià; Sopena, 2011). No entanto, as evidências científicas disponíveis mostram que grande parte dos estudos envolvem estratégias para a prevenção de pneumonias na população de pacientes em UTI, um grupo específico de pacientes que utilizam VM invasiva (Di Pasquale *et al*, 2016; Nair; Niederman, 2013; Roquilly *et al*, 2015).

Em 2001 o *Institute for Healthcare Improvement* (IHI) através de especialistas estabeleceu que pacientes em uso de VM são pacientes em alto risco para morbidade e mortalidade e com isso devem sofrer ações de intervenções prioritárias. Com isto, foram realizadas revisões da literatura que identificaram cinco elementos para o cuidado e prevenção de PAVM (Institute for Healthcare Improvement, 2012). Estes elementos são:

- Cabeceira elevada entre 30 e 45º;
- Interrupção diária da sedação e avaliação diária da prontidão para extubação;
- Profilaxia para prevenção de úlcera do estresse;
- Profilaxia para prevenção de trombose venosa profunda;

- Cuidado oral diário com clorexidina.

Estes elementos foram desenhados para serem aplicados conjuntamente formando um grupo integrado de medidas denominado *bundle*. Os *bundles*, conceito desenvolvido em 2001 pelo IHI, têm o intuito de promover melhorias nos processos de cuidados críticos assim como obter melhores níveis de confiabilidade no monitoramento e avaliação de tais processos e agravos, o que resultaria em melhorias de resultados. Por definição, um *bundle* é um conjunto de intervenções baseadas em evidências que, quando implementadas em conjunto a um determinado grupo de pacientes, permitem a obtenção de resultados significativamente melhores do que quando implementadas isoladamente (Resar *et al*, 2012). O *bundle* para prevenção de PAVM tem sido adotado por diversas instituições em todo o mundo.

A manutenção da cabeceira elevada tem sido associada a reduções nas taxas de PAVM. A recomendação é de manutenção da cabeceira entre 30 e 45º. Esta medida está provavelmente associada à redução do risco de aspiração de conteúdo gastrointestinal e da orofaringe para o trato respiratório inferior e, consequentemente, da ocorrência de pneumonia. Além disso, esta medida melhora a ventilação do paciente reduzindo o tempo de VM e assim o riso de desenvolver a infecção. Apesar de poucos estudos demonstrarem o real impacto desta medida nas taxas de PAVM é uma medida simples, de baixo custo e de fácil aplicação (American Thoracic Society, 2005; Institute for Healthcare Improvement, 2012; Klompas *et al*, 2014; Mastertorn *et al*, 2008).

A interrupção diária da sedação (teste de despertar espontâneo) tem sido associada à redução do tempo de uso da VM e, com isto, do risco de PAVM. A avaliação diária da prontidão para extubação está associada à extubação de um a dois dias antes quando comparado ao cuidado usual. Com esta medida os pacientes podem auxiliar no processo de extubação com o reflexo da tosse e controle de secreções, reduzindo o risco de aspiração deste conteúdo ao trato respiratório inferior (American Thoracic Society, 2005; Institute for Healthcare Improvement, 2012; Klompas *et al*, 2014).

A profilaxia para úlcera de estresse reduz o risco para sangramento gastrointestinal. Esta medida se justificaria pela redução do risco de pacientes aspirarem este conteúdo e desenvolver o processo infeccioso. No entanto, esta terapia aumenta o pH gástrico, aumentando o desenvolvimento de microrganismos no trato gastrointestinal e com isto o risco para pneumonias (Institute for Healthcare Improvement, 2012; Klompas *et al*, 2014; Tablan *et al*, 2004). Em consenso, a *Society for Healthcare Epidemiology of America* (SHEA) considera que esta medida não possui impacto nas taxas de PAVM não devendo, portanto, ser utilizada como rotina para redução desta complicação infecciosa (Klompas *et al*, 2014).

A profilaxia para prevenção de trombose venosa profunda não possui uma associação clara na redução das taxas de PAVM. De acordo com o IHI quando o *bundle* é aplicado em conjunto, incluindo esta medida, as taxas da infecção são reduzidas. No entanto, a SHEA não sugere a adoção desta medida no seu mais recente consenso como medida para prevenção de PAVM (Institute for Healthcare Improvement, 2012; Klompas *et al*, 2014).

O cuidado oral diário com clorexidina foi adicionado ao *bundle* de PAVM em 2010 pelo IHI após revisão da literatura. Placas dentária se desenvolve em pacientes ventilados mecanicamente devido à redução na mastigação mecânica e de saliva resultando em reservatórios de potenciais patógenos respiratórios que podem causar PAVM. O uso de clorexidina 0,12% é recomendado como fator de prevenção na formação de placas dentárias e do desenvolvimento de gengivite (Institute for Healthcare Improvement, 2012; Klompas *et al*, 2014; Tablan *et al*, 2004). A SHEA considera que as evidências disponíveis para esta medida são mais pronunciadas na prevenção de infecção do trato respiratório pós cirurgia cardíaca, podendo reduzir a incidência de infecção nesta população em até 30%. Dessa forma, para a SHEA esta medida é considera como uma abordagem especial de moderada evidência científica para uso em pacientes gerais (Klompas *et al*, 2014).

Outras estratégias específicas para a prevenção de PAVM, apesar de não constarem no *bundle* do IHI, foram desenvolvidas baseadas no conhecimento sobre a patogênese desta infecção. Evitar a intubação endotraqueal é uma medida considerada básica e de alta qualidade de evidência e está associada à redução no uso de VM invasiva (American Thoracic Society, 2005; Klompas *et al*, 2014). A minimização do acúmulo de secreções acima do tubo endotraqueal está baseada no uso de tubos de aspiração subglótica para pacientes com a probabilidade de requerer mais de 48 a 72 horas de intubação endotraqueal, pois permitem a sucção de secreções que se acumulam acima do *cuff* do tubo endotraqueal, interrompendo a aspiração de secreções para a árvore traqueobrônquica (American Thoracic Society, 2005; Klompas *et al*, 2014; Nair; Niederman, 2013; Torres *et al*, 2009). Ainda, a verificação periódica da pressão do *cuff* traqueal (acima de 20 cm H_2O) previne vazamentos de patógenos bacterianos que colonizam a cavidade oral para o trato respiratório inferior (American Thoracic Society, 2005; Mastertorn *et al*, 2008; Nair; Niederman, 2013; Torres *et al*, 2009).

A manutenção dos circuitos ventilatórios é uma medida que foi amplamente estudada e que possui poucas limitações e variações entre estudos. Esta medida se baseia na prática de não realizar a troca rotineira dos circuitos ventilatórios. Esta troca deve ser realizada apenas se o circuito estiver sujo ou com mau funcionamento. A mudança rotineira dos circuitos não possui impacto nas taxas de PAVM, além de aumentar os custos com o processamento deste

material (American Thoracic Society, 2005; Klompas *et al*, 2014; Mastertorn *et al*, 2008; Nair; Niederman, 2013; Torres *et al*, 2009).

A mobilização precoce dos pacientes e a realização de fisioterapia respiratória são medidas ainda não amplamente estudadas e que possuem variações nos resultados entre os estudos. No entanto, considera-se que estejam associadas à extubação precoce, redução no tempo de internação na UTI e aumento da taxa de retorno da função pulmonar independente (Klompas *et al*, 2014; Mastertorn *et al*, 2008).

Há, ainda, as medidas para prevenção de PAVM consideradas como abordagens especiais, que são intervenções que reduzem o tempo de duração da VM, tempo de internação e resultam, portanto, em menores taxas de mortalidade, mas para as quais ainda há dados insuficientes sobre os riscos associados. Dentre estas medidas encontram-se o uso de descontaminação seletiva da orofaringe para reduzir a carga microbiana do trato aerodigestivo; administração de probióticos profiláticos; uso de *cuff* de tubos endotraqueais de poliuretano ultrafino, que são *cuffs* que possuem melhor vedação contra a parede traqueal e que, dessa forma, permitiriam que um menor volume de secreção fosse aspirada ao trato respiratório inferior; controle automatizado da pressão do *cuff* do tubo endotraqueal; e uso de tubos endotraqueais impregnados com prata visando a redução da colonização bacteriana e inibição de formação de biofilme no tubo endotraqueal (Klompas *et al*, 2014; Nair, Niederman, 2013; Torres *et al*, 2009).

Além dessas estratégias, são consideradas medidas para prevenção de PAVM a higienização das mãos e o uso de técnicas recomendadas para o processamento dos materiais de assistência ventilatória, visando a redução das chances de transmissão cruzada de microrganismos entre os pacientes (Klompas *et al*, 2014; Mastertorn *et al*, 2008; Nair, Niederman, 2013; Tablan *et al*, 2004; Torres *et al*, 2009).

São muitas as recomendações existentes para a prevenção de PAVM descritas em diretrizes internacionais e sociedades profissionais. No entanto, são poucas as evidências claras e de boa qualidade para a prevenção de PNVM, sendo que muitas das medidas aplicadas nas instituições de saúde acabam sendo extrapolações provenientes de estudos realizados em pacientes em uso de VM (Pássaro; Harbarth; Landelle, 2016). Autores vêm realizando buscas na literatura e têm sustentado que as medidas para prevenção de PNVM devem ter como objetivo diminuir a colonização da orofaringe, reduzir o risco de broncoaspiração, reduzir a contaminação cruzada entre pacientes e ambiente, evitar a transmissão de microrganismos por aerossóis e modificar os fatores de risco do indivíduo (Di Pasquale *et al*, 2016; Flanders; Collard; Saint, 2006; Sopena, 2005).

Estudo recente que objetivou estabelecer um *bundle* para prevenção de PNVM revisou as recomendações das diretrizes do CDC e identificou dois grupos alvos de pacientes para prevenção de PNVM: os pacientes em pós-operatório e os pacientes que recebem nutrição enteral. Para estes dois grupos de pacientes o *bundle* estabeleceu as seguintes medidas visando a prevenção da PNVM:

- Manutenção da cabeceira da cama entre 30 e 45º, especialmente quando o paciente está se recuperando da anestesia ou enquanto há risco para aspiração;
- Promover higiene oral pelo menos duas vezes ao dia com antisséptico;
- Avaliar a membrana oral e notificar quebras de barreira mucosa;
- Instruir o paciente como utilizar o espirômetro de incentivo pelo menos uma vez por hora;
- Encorajar o paciente a se virar, tossir e respirar profundamente pelo menos uma vez por hora;
- Estimular o paciente a deambular assim que possível;
- Verificar a localização do tubo enteral antes de iniciar a administração da dieta;
- Verificar presença de resíduos antes de iniciar a dieta;
- Administrar profilaxia para úlcera péptica, a menos que seja contraindicado;
- Avaliar o status de imunização do paciente e administrar a vacina da influenza e pneumonia quando apropriado.

A construção e proposta deste *bundle* de cuidados vem a acrescentar na literatura um conhecimento sintetizado acerca das medidas que visam a prevenção das PNVM. No entanto, foi construído com base em uma diretriz que têm como grande parte de suas referências os estudos que foram desenvolvidos com os pacientes em uso de ventilação mecânica e que possuem fatores de risco muito específicos. Revisões da literatura que também tentam propor medidas para a prevenção de PNVM vêm encontrando resultados similares aos propostos pelos autores do *bundle*, também incluindo resultados provenientes de estudos com pacientes em uso de VM, trazendo especialmente a importância da prevenção de aspirações, higiene oral e mobilização dos pacientes.

A colonização da orofaringe com microrganismos hospitalares, que ocorre após a internação, é considerada como um importante fator para o desenvolvimento de PNVM. Sendo assim a higiene oral com antisséptico é considerada uma medida para a prevenção desta complicação infecciosa (Flanders; Collard; Saint, 2006; Pássaro; Harbarth; Landelle,

2016). A prevenção de fatores de risco que aumentam o risco de microaspirações, tais como a disfagia, condição que afeta com frequência idosos e pacientes que sofreram acidentes vasculares encefálicos, através do seu diagnóstico e tratamento, também é considerada medida importante na prevenção de PNVM (Pássaro; Harbarth; Landelle, 2016). A manutenção da cabeceira entre 30 e 45º, especialmente durante as refeições em pacientes com risco de broncoaspiração e a mudança de decúbito periódica em pacientes sem mobilidade espontânea, devem ser considerados neste grupo de pacientes. Ainda, a promoção de deambulação progressiva é outra importante medida na prevenção de PNVM. Para pacientes que não podem deambular, a fisioterapia respiratória deve ser instituída com o objetivo de manter a eficácia da tosse e prevenir atelectasias (Mastertorn *et al*, 2008; Sabriá, Sopena; 2011; Tablan *et al*, 2004). O uso de tubos para alimentação enteral também desempenha um papel importante no desenvolvimento das pneumonias, uma vez que aumentam o risco de aspiração de conteúdo gástrico. A manutenção do paciente em posição semi-recumbente pode reduzir as chances de aspiração durante a administração das dietas (American Thoracic Society, 2005; Mastertorn *et al*, 2008; Tablan *et al*, 2004).

Além disso, para prevenir PNVM as medidas devem focar na modificação de fatores de risco individual, como a desnutrição. Pacientes com hipoalbuminemia, um indicador de estado nutricional ruim, devem ser considerados como risco para o desenvolvimento de PNVM e devem ser monitorados. Ainda, sempre que possível, o uso de medicamentos imunossupressores, antibióticos de amplo espectro e tubos nasogástricos devem ser evitados (Sabrià; Sopena, 2011).

3.7 FATORES DE RISCO PARA PNEUMONIA RELACIONADA À ASSISTÊNCIA À SAÚDE

Parcela substantiva das evidências científicas acerca dos fatores de risco para as pneumonias hospitalares são provenientes de estudos realizados com pacientes críticos em uso de VM (Humphreys, 2008; Russell *et al*, 2016; Zhang; Duan, 2015). Os estudos acerca dos fatores de risco para PNVM são, em sua maioria, realizados com grupos específicos de pacientes, como aqueles submetidos a cirurgias cardíacas ou abdominais, imunossupressos ou idosos (Sabrià; Sopena, 2011; Sopena *et al*, 2014).

Os fatores de risco para PNVM são classificados de diversas formas pelos autores, tais como: fatores de risco intrínsecos e extrínsecos (Sopena; Sabrià, 2005); fatores relacionados

ao paciente ou a manobras terapêutica (Edis *et al*, 2009); ou relacionados ao paciente, intervenções médicas e intervenções invasivas (Edis *et al*, 2009).

A ATS e o CDC trazem em suas diretrizes os fatores de risco para pneumonias hospitalares que são considerados modificáveis e que devem ser alvo de melhoria de gestão do cuidado nas instituições de saúde. Os fatores de risco levam em consideração a patogênese da infecção e estão descritos no Quadro 2.

Quadro 2 – Fatores de Risco para PNVM descritos nas diretrizes internacionais.

Categoria	Fator de Risco
Fatores que aumentam a colonização da orofaringe e estômago	Administração de antimicrobianos Admissão em UTI Presença de doença pulmonar crônica
Condições que favorecem a aspiração para o trato respiratório ou refluxo do trato gastrintestinal	Intubação endotraqueal de repetição Inserção de tubo nasogástrico Uso de antagonistas da histamina$_2$ e antiácidos Posição supina Coma Procedimentos cirúrgicos envolvendo cabeça, pescoço, tórax ou abdômen superior Imobilização devido a trauma
Condições que favorecem o uso de dispositivos invasivos	Uso prolongado de dispositivos de assistência ventilatória que podem ser contaminados pelas mãos dos profissionais de saúde
Fatores do hospedeiro	Idade avançada Desnutrição Condições de base severas, incluindo imunossupressão

American Thoracic Society. Am J Respir Crit Care Med. 2005 Feb 15;171(4):388-416. Klompas M et al. Infect Control Hosp Epidemiol. 2014 Aug;35(8):915-36. Healthcare Infection Control Practices Adviory Committee. Respir Care. 2004 Aug;49(8):926-39.

Algumas revisões não sistemáticas de literatura foram realizadas sobre o tema das PNVM. Estas revisões trazem aspectos gerais sobre a epidemiologia, diagnóstico, prevenção, tratamento e fatores de risco das PNVM. Os principais fatores de risco considerados nas revisões de literatura estão descritos no Quadro 3.

Quadro 3- Fatores de Risco para PNVM descritos nas revisões de literatura.

Classificação	Fatores de Risco	Referência

Fatores de Risco relacionados ao paciente	Idade avançada (acima de 60 anos) Presença de doenças crônicas (doença renal crônica, anemia, neoplasia, doença pulmonar obstrutiva crônica) Desnutrição Imunossupressão Depressão do nível de consciência Internação hospitalar prévia (últimos 30 dias)	Di Pasquale M, 2016 Nair, 2013 Torres, 2009 Flanders, 2006 Sopena 2011
Fatores de Risco relacionados a intervenções invasivas	Procedimentos terapêuticos, como cirurgia torácica e abdominal Posição supina Uso de tubo nasogástrico Uso de tubo nasoentérico Tratamento antimicrobiano prévio Tratamento imunossupressor Uso de medicação supressora do ácido gástrico Uso de equipamentos de assistência ventilatória	Di Pasquale M, 2016 Nair, 2013 Torres, 2009 Flanders, 2006 Sopena 2011

Entre os fatores relacionados às intervenções médicas merecem destaque aqueles que aumentam a colonização da orofaringe e gástrica, como o uso prévio de antimicrobianos, a elevação do pH gástrico pelo uso de antiácidos ou agentes bloqueadores de histamina$_2$ e contaminação cruzada pela manipulação ou falhas no processamento de equipamentos respiratórios, como nebulizadores e umidificadores (Nair; Niederman, 2013).

Ainda, dentre os fatores que aumentam o risco de microaspirações destacam-se a posição supina e o uso de tubo nasogástrico e nasoentérico. Procedimentos cirúrgicos que envolvem cabeça e pescoço e imobilização por trauma são também fatores que aumentam o risco de microaspirações (Nair; Niederman, 2013; Torres *et al*, 2009).

Os estudos originais que investigaram os fatores de risco para as PNVM encontraram como fatores relacionados ao paciente a idade avançada; presença de doenças de base como neoplasias, doença renal crônica, anemia, doença pulmonar obstrutiva crônica, insuficiência cardíaca, diabetes, neutropenia e obesidade; desnutrição, tabagismo, alcoolismo e depressão do nível de consciência. Estes estudos citam o risco para aspiração, que inclui pacientes apresentando estados de confusão mental por qualquer causa, especialmente doenças neurológicas, e pacientes em posição supina como um importante fator relacionado ao paciente para PNVM. Entre os fatores de risco relacionados a intervenções médicas e invasivas estão as cirurgias torácicas, abdominais e de cabeça/pescoço, o uso de tubos nasogástricos e nebulizador, a presença de traqueostomia, a intubação endotraqueal prévia, a realização de nutrição parenteral total, transfusões sanguíneas, os tratamentos com

medicamentos imunossupressivos, o tratamento prévio com antibióticos, o uso de bloqueadores H_2 e inibidores da bomba de prótons e o tempo de internação prolongado (Edis *et al*, 2009; Ohi *et al*, 2004; Sopena; Sabrià, 2005; Sopena *et al*, 2014).

4 JUSTIFICATIVA

Diversos estudos têm demonstrado a importância epidemiológica que as pneumonias hospitalares representam às instituições de saúde (Davis; Finley 2012; DiBiase *et al*, 2014; Magill *et al*, 2014). É sabido que estas infecções, tanto as PAVM quantos as PNVM, são infecções graves e que estão associadas a uma elevada morbidade, mortalidade e aumento de custos hospitalares (Sabrià; Sopena, 2011). Porém, grande parte dos estudos já desenvolvidos e publicados sobre as pneumonias hospitalares e seus fatores preditores, etiológicos e medidas preventivas, sejam eles estudos observacionais, revisões sistemáticas ou revisões não sistemáticas, foram realizados em pacientes críticos em uso de VM (Bo *et al*, 2014; Labeau *et al*, 2011; Lerma *et al*, 2014; Muscedere *et al*, 2011; O'Grady; Murray; Ames, 2012; Rello *et al*, 2011; Russell *et al*, 2016; Zhang; Duan, 2015). Baseados nestes estudos, diretrizes e consensos de especialistas, tanto à nível nacional quanto internacional, já foram realizadas (American Thoracic Society, 2005; Klompas *et al*, 2014; Masterton *et al*, 2008; Tablan *et al*, 2004). Através de todo o conhecimento existente para a prevenção de PAVM e a utilização destas diretrizes, esta infecção tem reduzindo suas taxas de incidência nos últimos anos nas instituições de saúde.

Em contrapartida, a incidência das PNVM vem aumentando, sendo responsáveis por aproximadamente dois terços das pneumonias hospitalares (Magill *et al*, 2014). As informações quanto a fatores de risco e medidas de prevenção utilizados para PNVM têm sido amplamente extrapoladas de experiências vindas de estudos realizados em UTI (Dalhoff; Ewig, 2013; Klompas, 2016; Lynch, 2001; Nair; Niederman, 2013; Ottosen; Evans, 2014; Sabrià; Sopena, 2011; Torres *et al*, 2009). Entretanto, a ausência de intubação e VM diferenciam a etiologia e fisiopatologia nestes grupos de pacientes, o que torna esta uma entidade distinta de infecção do trato respiratório (Di Pasquale *et al*, 2016). Ainda, os pacientes em unidades de internação não estão expostos a manobras tão agressivas quanto aqueles recebendo VM, as mudanças na flora da orofaringe são menores e a flora comunitária persiste por períodos mais prolongados. Estes fatores sugerem que a etiologia e abordagens terapêuticas nestes dois grupos devem ser diferentes e não são totalmente comparáveis (Edis *et al*, 2009).

Não foram encontradas na literatura revisões sistemáticas que sintetizassem o conhecimento acerca dos fatores de risco para PNVM. Apenas uma revisão não sistemática da literatura foi encontrada com o objetivo de avaliar a evidência existente em relação a

patogênese, diagnóstico, tratamento e prevenção das PNVM, no entanto, mesmo esta revisão, incluiu dados de pacientes em uso de VM (Di Pasquale, 2016).

O desenvolvimento de uma revisão sistemática que possa identificar, sumarizar e ainda quantificar os fatores preditores existentes para PNVM auxiliará no entendimento destes fatores e identificar em quais é possível que, como profissionais de saúde, possamos atuar visando o desenvolvimento de estratégias de prevenção e controle que reduzam a morbidade dos pacientes, custos associados para o sistema de saúde e mortalidade associada à PNVM.

5 OBJETIVO

Identificar, quantificar e sumarizar a evidência existente na literatura sobre os fatores preditores de pneumonia hospitalar não associada à ventilação mecânica (PNVM) em pacientes adultos internados em unidades de cuidados não intensivos.

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7 ARTIGO

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Título:

PREDICTOR FACTORS FOR THE DEVELOPMENT OF NON-VENTILATED HOSPITAL-ACQUIRED PNEUMONIA: SYSTEMATIC REVIEW AND METANALYSIS

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ABSTRACT

This systematic review aimed to identify, quantify and summarize the evidence on predictor factors for non-ventilated hospital acquired pneumonia (NVHAP) in adult patients. Systematic literature search was undertaken on PubMed, Embase, Scopus and LILACS. Case-control and cohort studies were included according to previously defined criteria. Metanalysis was performed for factors available from more than one study. National Institute of Health assessment tool was applied to assess quality of the studies. A total of 11,380 studies were found and 35 met inclusion criteria. This review found 269 different risk factors, of which 58 were included in metanalysis with 33 predictor factors being significantly associated with NVHAP. When sensitivity analysis was performed without poor quality studies 22 significant risk factors remained associated to NVHAP. Literature shows that there are 22 risk factors for NVHAP and there is a lack of good quality studies to establish the association of risk factors

with NVHAP.

Introduction

Hospital acquired pneumonia (HAP) is one of the most prevalent healthcare associated infections and is associated to a high morbidity and mortality worldwide. It is estimated that HAP is responsible for approximately 15 to 20% of all infections in hospitals, with more than two thirds happening in patients not in use of mechanical ventilation [1-3]. Non-ventilated hospital acquired pneumonia (NVHAP) is associated to longer length of stay, need of intensive care unit (ICU) hospitalization and mechanical ventilation, besides been associated to high hospital costs and higher mortality [4-9].

The knowledge about the predictor factors for the development of NVHAP have been widely extrapolated from the evidence gained with studies where the population are critically ill patients in mechanical ventilation use [3]. However, the absence of intubation and mechanical ventilation differentiates the etiology, pathophysiology and predictor factors in these two groups of patients, which makes NVHAP a distinct entity of respiratory tract infection [10]. Thus, this systematic review aimed to identify, quantify and summarize the existing literature evidence on the predictor factors for NVHAP in adult patients admitted to non-intensive care units.

Materials and Methods

Protocol and Registration

This review followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines in its conduction [11, 12]. The search strategy was organized according to the PICOS acronym, where population = adult hospitalized patients, intervention = risk/predictor factors, comparison = none, outcome = NVHAP and study design = case-control or cohort study. The systematic review protocol was published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017060670).

Literature Search

A systematic search of Medline (via PubMed), Embase, Scopus and LILACS was

performed in March 2017 to identify all related studies. The following keywords and/or corresponding medical subject heading terms were used: nosocomial infection or hospital infection or healthcare associated infection or cross infections; and pneumonia or hospital acquired pneumonia or healthcare associated pneumonia or respiratory tract infection; and risk factors or associated factors. The Cochrane Database of Systematic Reviews and the Centre for Reviews and Dissemination were reviewed for similar systematic reviews. Manual searched of reference lists of relevant systematic reviews and included articles were also conducted. The search was actualized in February 2018.

Eligibility Criteria

The studies were included if they (1) were retrospective or prospective cohorts or case-control studies assessing NVHAP risk factors; (2) involved adult participants; (3) diagnosed the NVHAP according to the definition proposed by the Centers for Disease Control and Prevention (CDC) or used a similar definition; (4) were performed with patients hospitalized in a clinical/medical, surgical or trauma non-intensive care unit; (5) reported estimates (or enough data to calculate) of odds ratios (OR), relative risks (RR), or hazard ratios (HR) with their corresponding 95% confidence intervals (CIs); and (6) compared patients with NVHAP with patients without such infectious complication. We excluded studies that (1) were performed in patients in use of mechanical ventilation or intubation; (2) were performed in patients with the diagnose of ventilator-associated pneumonia; and (3) studies developed in patients with community-acquired pneumonia. No publication date or language restrictions were applied.

Screening and Data Extraction

Titles and abstracts of the articles identified from the search strategy were independently screened by three reviewers (where SAL reviewed all studies, while CHD and FA reviewed 50% of the studies each) to determine relevance and general adherence to eligibility criteria. The full text of the selected articles was obtained and independently screened by the same three reviewers (SAL, CHD and FA) using a standardized form to assess suitability for inclusion in the final review against the criteria defined above. Disagreements between the reviewers were solved by a forth reviewer (PKZ). Two independent authors (SAL and PKZ) were designed for data extraction using a standardized form developed by the authors of this review. The following information were extracted from the studies that met the inclusion criteria: authors, year of publication, country where the

study was performed, study design, sample and setting, type of population, and NVHAP predictors. For each predictor data regarding relative effect measures (OR, RR or HR) were collected. Disagreements in this phase were solved by consensus.

Assessment of Risk of Bias

Two reviewers (SLF and RSK) independently assessed the risk of bias. Because only cohort and case-control studies met the inclusion criteria, risk of bias was assessed according to the instrument developed by the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort studies and Case-control studies. In case of disagreements a third reviewer (PKZ) was called to make a final decision. The authors of this systematic review defined a criterion to classify each study as good, fair or poor. Cohort studies that did not present a clear criteria regarding NVHAP definition, as the one proposed by the CDC for surveillance of healthcare associated infections, were considered as having a poor quality rate. Also were rated as poor those cohort studies that did not have a clear definition for the risk factors being studied and did not present an analysis adjusted by, at least, gender and age. Considering these last two characteristics, if a cohort study was assigned as a "no" for just one of them, it was rated as fair. All the others were rated as good. For case-control studies the same criteria were used, with one addition regarding the selection of controls: studies where the controls were not selected or recruited from the same or similar population that gave rise to the cases were also considered as having poor quality rate.

Statistical Analysis

Meta-analysis was performed for all predictors where OR estimates with 95% CI (or enough data to calculate) were available for more than one study. In studies where associations between predictor and NVHAP were presented through multiple sequentially-adjusted models, the effect estimate and 95% CIs from the most fully-adjusted model was used in the meta-analysis. For each predictor, studies were weigthed by the Mantel-Haenzel method and then pooled using random effects model with DerSimonian and Laird variance estimator. Sensitivity analysis was conducted using the results from the quality assessment: studies classified as with poor quality were excluded from the metanalysis. Metanalysis results were presented as forest plots for both with and without poor quality studies. Studies that present their results using RR or HR only were just included in the narrative synthesis. All statistical analysis was performed using Meta R Package (https://CRAN.R-project.org/package=meta).

Results

The systematic literature search returned 16,138 studies, which was reduced to 11,380 unique citations after removal of duplicates. Titles and abstracts were read and 98.8% of the papers were excluded for not being relevant to the study question. In total, 133 studies underwent full-text review, 35 were included in the qualitative analysis and 33 were eligible for inclusion in the metanalysis. Two studies reported only relative risks or hazard ratios, not allowing the extraction of the crude data for OR calculations and were therefore excluded from the metanalysis (Figure 1).

Descriptive characteristics of the 35 studies included in the analysis are presented in Table 1. In brief, of the 33 papers included in the metanalysis, eight were case-control studies and 25 were cohort studies. Thirty-two studies were published in English and one in Spanish. More than half of the studies (51.5%) were published before 2010. The populations found in the studies were general patients, elderly, stroke patients and surgical patients. The two studies excluded from the metanalysis were developed in the elderly population and one of them was published in French.

The quality rate of all individual studies is shown in Table 1 and detailed informations are described in Supplementary material (Supplementary Table 1 and Supplementary Table 2). Fourteen (42.4%) studies were rated as poor for not clearly defining the criteria for NVHAP and 15 (45.5%) were considered fair for either not performing the multivariate analysis or not adjusting statistically for age and gender. No study was rated as poor for not having a clear definition for the risk factors being studied and not presenting the adjusted analysis.

Overall, 269 different predictor factors were reported in, at least, one study. From these, 58 were included in the metanalysis. Results for age and gender, for being consolidated in the literature as factors associated to many outcomes, are shown separately (Figure 2 and Figure 3). Older patients (>70 years) and men were significantly (p-value<0.05) associated with the development of NVHAP. Regarding the other 56 predictor factors, 32 (57.1%) were found to be significantly associated to the development of NVHAP (Figure 4; Supplementary Figure 1 and Supplementary Figure 2). While the vast majority are risk factors (OR ranged from 0.75 to 8.71), only dyslipidemia (OR = 0.84, 95% CI 0.82; 0.86) was found to be a protective factor.

As a sensitivity analysis, metanalysis were performed without the studies rated as poor in quality assessment. After this analysis, the following predictor factors remained significantly associated to the development of NVHAP: albumin <3.0 (mg/dL), alcohol use, antibiotic therapy, blood loss, chronic pulmonary disease, congestive heart failure, depression of consciousness, dysphagia, enteral tube feeding, full mobility impairment, malnutrition, nasogastric tube, parenteral nutrition, partial mobility impairment, previous hospital admission, previous ICU admission, previous pneumonia, sedative use, severe National Institute of Health Stroke Scale (NIHSS) score>4), smoking within 1 year, surgery acuity (emergent/urgent), weight loss >10% in last 6 months. Male sex was not significantly associated to the development of NVHAP after the sensibility analysis (Figure 5; Supplementary Figure 3, Figure 4 and Figure 5). The two hundred and eleven predictor factors that were described only once among studies were, therefore, excluded from this systematic review.

Discussion

This systematic review, conducted to identify, quantify and summarize the predictor factors for NVHAP, returned that 269 different factors have been investigated in the literature. Among them, 58 were evaluated in more than one study and were, therefore, included in a metanalysis with 33 being statistically associated to NVHAP. The sensitivity analysis performed showed that after removing the studies rated as poor in the quality assessment, only 22 out of 33 risk factors were in fact associated to the development of NVHAP.

Age is a factor commonly associated with many different comorbidities. In our meta-analysis it was observed that age greater than 70 years was significantly associated with NVHAP. This association may be explained by the fact that elderly patients generally have comorbidity illnesses, longer hospital stay, physical impairment, physiological and immunological changes that are inherent to the aging process, rather than for the age itself [15, 40]. Therefore, this review suggests that, a study aiming to evaluate the risk factors for NVHAP should consider age into their multivariate models. Also, male was considered statistically associated to NVHAP. It is hypothesized that this association may be attributable to the higher prevalence of smoking, pre-existing pulmonary disease and other comorbidities among men [26].

Depression of consciousness, dysphagia, full and partial mobility impairment and sedative use were significantly associated to NVHAP. These risk factors are closely related to

the aspiration of secretions from the upper airway into the lower respiratory tract, one of the most important mechanisms for HAP described in the literature [47, 48]. In patients not submitted to mechanical ventilation, aspirations occur because of the impairment of the cognitive function that decreases the ability of the patient to protect the airway posing the patient at a greater risk for aspiration [34, 37, 47-50].

The NIHSS, a clinical stroke assessment tool that evaluates and documents neurological status in stroke patients, predicts stroke severity and both short and long-term outcomes for stroke patients [51]. This review shows that patients with a NIHSS score >4 was statistically associated to NVHAP. In fact, those patients have a less favorable clinical outcome and a high likelihood of functional dependence, being also associated with a deteriorated level of consciousness and decreased bulbar reflex, increasing the risk for aspirations [21, 24-29, 30, 37, 42]. The use of enteral feeding and nasogastric tube have been related to an increase in gastric pH resulting in gastric colonization, and also putting patients in risk to aspiration of gastric content, mainly when they are kept in the supine position [47, 48].

The development of NVHAP following emergent/urgent surgery seems to be related to the use of intubation and ventilation, that may continue to be a risk for pneumonia even after extubation [52]. However, little is described in the literature about the reasons emergent/urgent surgery may be a risk factor for NVHAP.

Previous antibiotic therapy, previous hospital stay and previous ICU stay were significantly associated to NVHAP. Some studies describe these risk factors as a reflection of the patient's susceptibility to infections. Also, previous antibiotic therapy as well as previous hospitalization may select gram-negative nosocomial bacteria colonizing the patient's upper airway and that can reach the lower respiratory tract, leading to the development of pneumonia [14, 19, 47-49].

Smoking is considered to be a risk factor for many diseases and for HAP smoking at the time of hospitalization may be a risk by enhancing the airway colonization by nosocomial pathogens [48]. However, in this systematic review the association between smoking history and NVHAP was not significant. It may be due to the fact that the majority of studies that assessed smoking history did not clearly state what was considered as history. Maybe they considered ex-smokers as history of smoking [31, 32, 37, 42]. On the other hand, those studies evaluating patients smoking during the last year found that it was significantly associated to the development of NVHAP [31, 32, 37, 42].

It is notable that most of the risk factors found to be significantly associated to NVHAP, such as advanced age, albumin <3,0 mg/dL, alcohol use, chronic pulmonary disease, congestive heart failure, malnutrition and weight loss >10% in the last six months are related to patient's general health and may only be controlled, but not changed.

Anemia, ASA score ≥3, atrial fibrillation, blood transfusion, coronary disease, dyslipidemia, fatal/ultimately fatal underlying disease, liver disease, nebulization and procedure time ≥2 hours were not statistically associated to NVHAP. It is of note that these factors in the first analysis were associated to NVHAP, however after the sensitivity analysis was performed this significance disappeared. Therefore, these factors need more good quality studies to demonstrate its association to NVHAP.

This study has some limitation. First, some of the ORs used in the metanalysis were not adjusted, because many studies reported only data from univariate analysis rather than multivariate statistics; likewise, some studies may have chosen not to report non significant results or not adjust for non significant factors.

Second, different definition to identify NVHAP were used among the individual studies. In particular, clinical diagnosis was used to define NVHAP. It is known that clinical diagnosis is based on the judgment, sometimes subjective, of the physician and should be used to guide the treatment of the patient rather than to define NVHAP. The definition of NVHAP with a criterion, like the one from the CDC, is used to determine in an objective and standardized way the presence of an infection. Therefore, many patients with a clinical diagnosis of NVHAP may not have NVHAP after applying the objective criteria. The lack of a good, valid and reliable definition for NVHAP may have biased the results of this study. Finally, the high heterogeneity of the population included in the review did not allow subgroup analysis.

Despite the limitations, this study has some strengths. First, it is the first systematic review and metanalysis performed that quantitatively summarized the predictor factors for NVHAP. Second, a search strategy based on computer assisted and manual search was performed, ensuring that, as far as possible, no relevant studies were omitted.

Conclusion

This metanalysis identified albumin <3.0 (mg/dL), alcohol use, antibiotic therapy, blood loss, chronic pulmonary disease, congestive heart failure, depression of consciousness, dysphagia, enteral tube feeding, full mobility impairment, malnutrition, nasogastric tube,

parenteral nutrition, partial mobility impairment, previous hospital admission, previous ICU admission, previous pneumonia, sedative use, severe NIHSS score 9>4), smoking within 1 year, surgery acuity (emergent/urgent), weight loss >10% in last 6 months as predictor factors for NVHAP. It also demonstrates that more studies are needed to evaluate those factors that could not be associated to NVHAP due to poor quality rating and to consolidate those factors that turned not to be associated to NVHAP after the sensitivity analysis. Given the implications of NVHAP to hospitalized patients, the increased knowledge of the significant predictor factors for the development of this infectious complication will allow better identification of those patients most likely to develop NVHAP.

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Table 1 - Characteristics of the 35 eligible studies

Reference (year)	Country	Study design	Patient population	Age			Gender		No of patients with NVHAP	No of patients without NVHAP	Quality assessment
				General	NVHAP	no NVHAP	Male	Female			
Gomez, 1995[13]	Spain	CC	General		58±14		132 (63.5)	76 (36.5)	104	104	☐
Barreiro-Lopez, 2005[14]	Spain	CC	General		70±13	70±12.8	96 (71.6)	38 (28.4)	67	67	☐
Fortaleza, 2009[15]	Brazil	CC	General		70	57.4	50 (37.9)	82 (62.1)	66	66	☐
Herzig, 2009[16]	USA	C (P)	General	54 [18-107]			23,801 (37.3)	40,077 (62.7)	2,219	61,659	●
Sopena, 2014[17]	Spain	CC	General		70±14.46		86 (72.3)*	33 (27.7)*	119	238	▼
Micek, 2016[4]	USA	CC	General		57.5±15	57.5±14.9	475 (54.6)	395 (45.4)	174	696	☐
Bourdel-Marchasson, 2001[18]	France	C (P)	Elderly	86.3±7.6			87 (21.6)	315 (78.4)	30	372	☐
Rothan-Tondeur, 2003[19]	France	CC	Elderly		87 (67-100)	85 (65-100)	75 (33.3)	150 (66.7)	75	150	☐
Burton, 2014[20]	UK	C (P)	Elderly	82±8			539 (41.4)	763 (58.6)	76	1,226	☐
Ewan, 2015[21]	USA	C (P)	Elderly		83.5	80.6	29 (32.2)	61 (67.8)	10	80	☐
Dziedzic, 2006[22]	Poland	C (R)	Stroke	69.7±12.6	75.6±10.1	69±12.7	320 (45.4)	385 (54.6)	74	631	☐
Ovbiagele, 2006[23]	USA	C (P)	Stroke	--	--	--	297 (45)	363 (55)	66	594	▼
Sellars, 2007[24]	Scotland	C (P)	Stroke	67.9±13.9	75.9±11.4	64.9±13.9	205 (63.7)	117 (36.3)	78	244	☐
Chumbler, 2010[25]	USA	C (R)	Stroke	71.4±13.2			784 (59.5)	533 (40.5)	96	1,221	▼
Hoffmann, 2012[26]	Germany	C (P)	Stroke	71.2 (13.1)			7,759 (50.6)	7,576 (49.4)	1,104	14,231	▼
Ji, 2013[27]	China	C (P)	Stroke	66 (56-74)			5,430 (61.6)	3,390 (38.4)	1,007	7,813	●
Masrur, 2013[28]	USA	C (P)	Stroke	73 [61-82]	78 [66-85]	73 [60-82]	150,095 (47.8)	163,912 (52.2)	17,906	296,101	▼
Brogan, 2015[29]	Australia	C (R)	Stroke	--	--	--	271 (56.5)	209 (43.5)	60	420	▼
Sari, 2016[30]	Indonesia	C (R)	Stroke	58.4±10.1			55 (52.4)	50 (47.6)	24	81	☐
Likosky, 2015[31]	USA	C (P)	Surgical (cardiac)	25-95			11,878 (73.4)	4,304 (26.6)	576	15,606	▼
Strobel, 2016[32]	USA	C (P)	Surgical (cardiac)		66.4±10.9	65.3±10.3	11,883 (73.9)	4,201 (26.1)	531	15,553	▼

Mohri, 2008[33]	Japan	C (P)	Surgical (gastric cancer)	68 (22-91)			359 (67.8)	170 (32.2)	20	509	□
Park, 2013[34]	Japan	C (R)	Surgical (gastric cancer)	63.2±9.6			1,116 (67.9)	527 (32.1)	38	1,605	●
Garibaldi, 1981[35]	USA	C (P)	Surgical (general)	--	--	--	198 (38.1)	322 (61.9)	91	429	▼
Iwamoto, 1993[36]	Japan	C (R)	Surgical (general)	--	--	--	--	--	30	4,380	▼
Arozullah, 2001[37]	USA	C (P)	Surgical (general)		68.9±10	61.2±13.3	153,214 (95.3)	7,536 (4.7)	2,466	158,339	□
Shiono, 2007[38]	Japan	C (R)	Surgical (lung cancer)	64 (22-90)			1,175 (64)	662 (36)	58	1,779	▼
Yamada, 2010[39]	Japan	C (R)	Surgical (lung cancer)	64.9 (8.7)			430 (68.7)	196 (31.3)	40	586	▼
Wang, 2014[40]	China	C (R)	Surgical (lung cancer)		60 [26-79]		338 (66.1)	173 (33.9)	15	496	□
Oh, 2014[41]	USA	C (R)	Surgical (neurologic)	58±13	72±9	58±13	133 (28.7)	331 (71.3)	6	458	▼
DeFreitas, 2012[42]	USA	C (P)	Surgical (vascular)	--	--	--	25,971 (63.8)	14,698 (36.1)	764	40,210	▼
Pannuti, 1992[43]	USA	CC	BMT	--	--	--	--	--	55	55	□
Zhu, 2015[44]	China	C (P)	Cardiac	60.7±14.3			4,814 (55.6)	3,843 (44.4)	550	8,107	●
Minakuchi, 2014[45]	Japan	C (R)	Hemodialysis		76.8±1.74	62.4±2.94	13 (68.4)*	6 (31.6)*	19	337	□
Tumbarello, 2001[46]	Italy	CC	HIV		34.1±6.2	33.3±4.4	93 (73.8)	33 (26.2)	42	84	□

CC = case-control study; C (P) = cohort study (prospective); C (R) = cohort study (retrospective); USA = United States of America; UK = United Kongdom; BMT = bone marrow transplant; ● good quality study; □ fair quality study; ▼ poor quality study
*data only available for cases

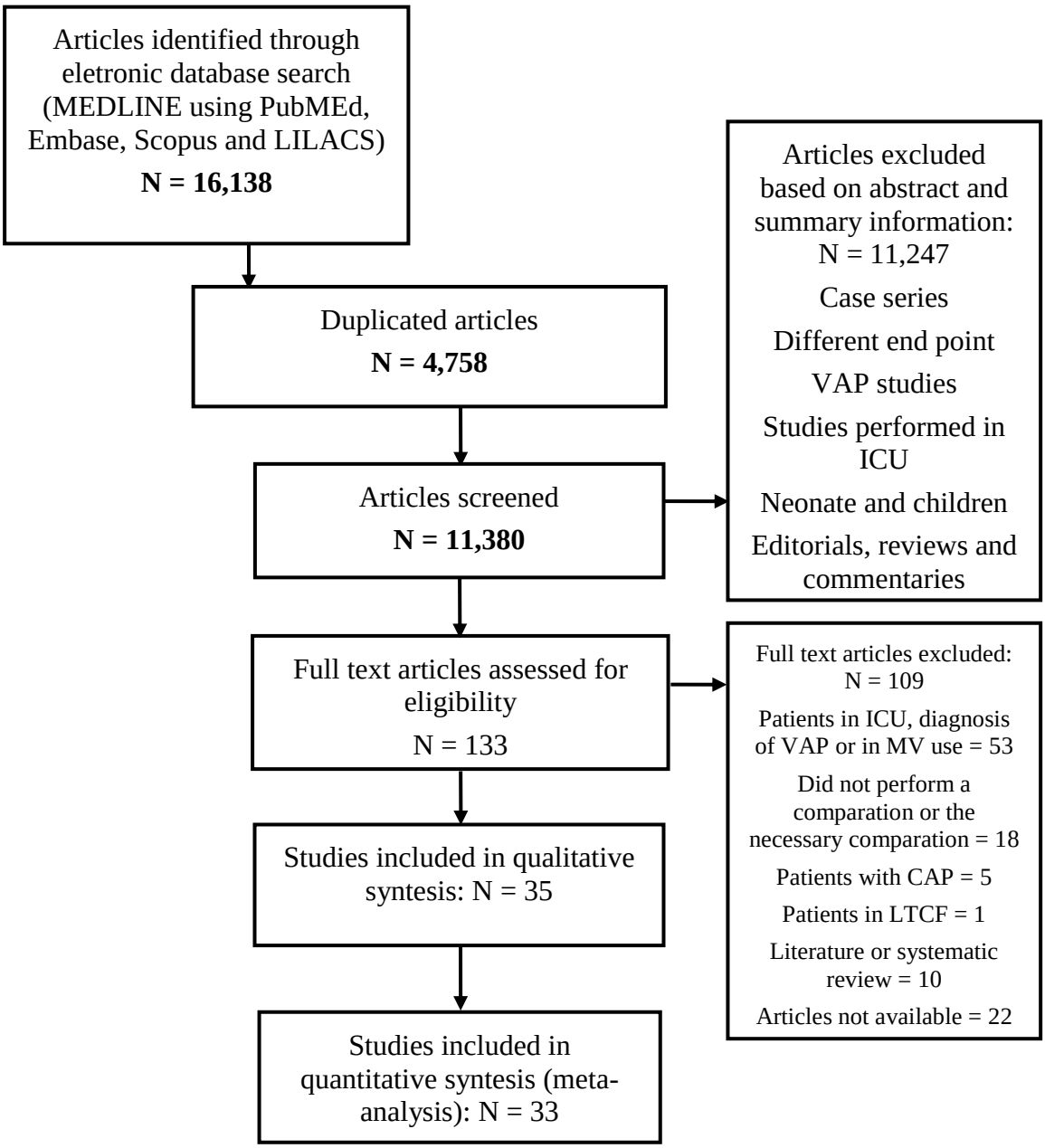


Figure 1. Systematic review flow diagram.

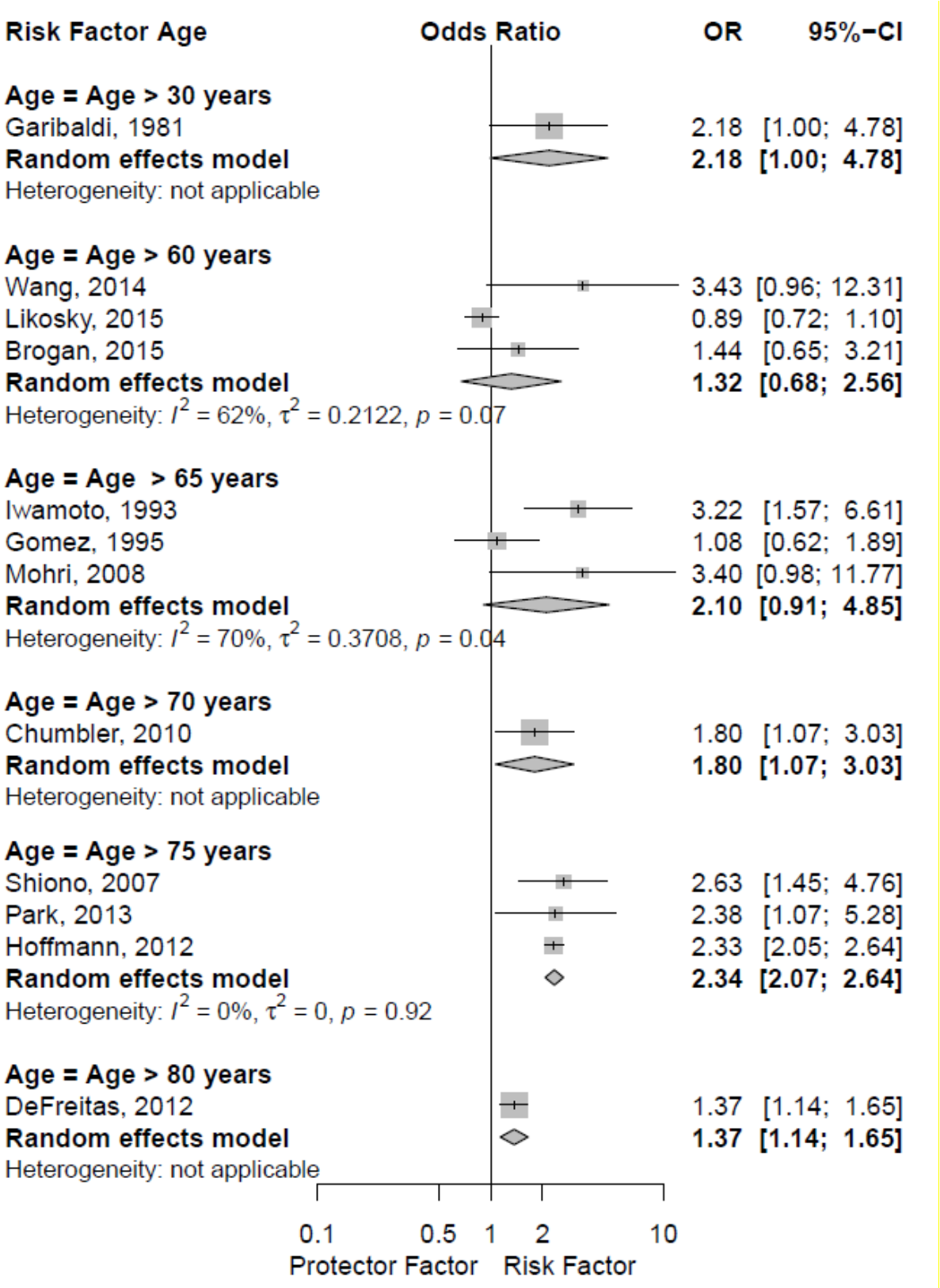


Figure 2. Forest plot of the metanalysis for age.The width of the horizontal line represents the 95% confidence interval (CI) of the individual studies, and the square represents the proportional weight of each study. Diamonds represent the pooled odds ratios (ORs) and 95% CI.

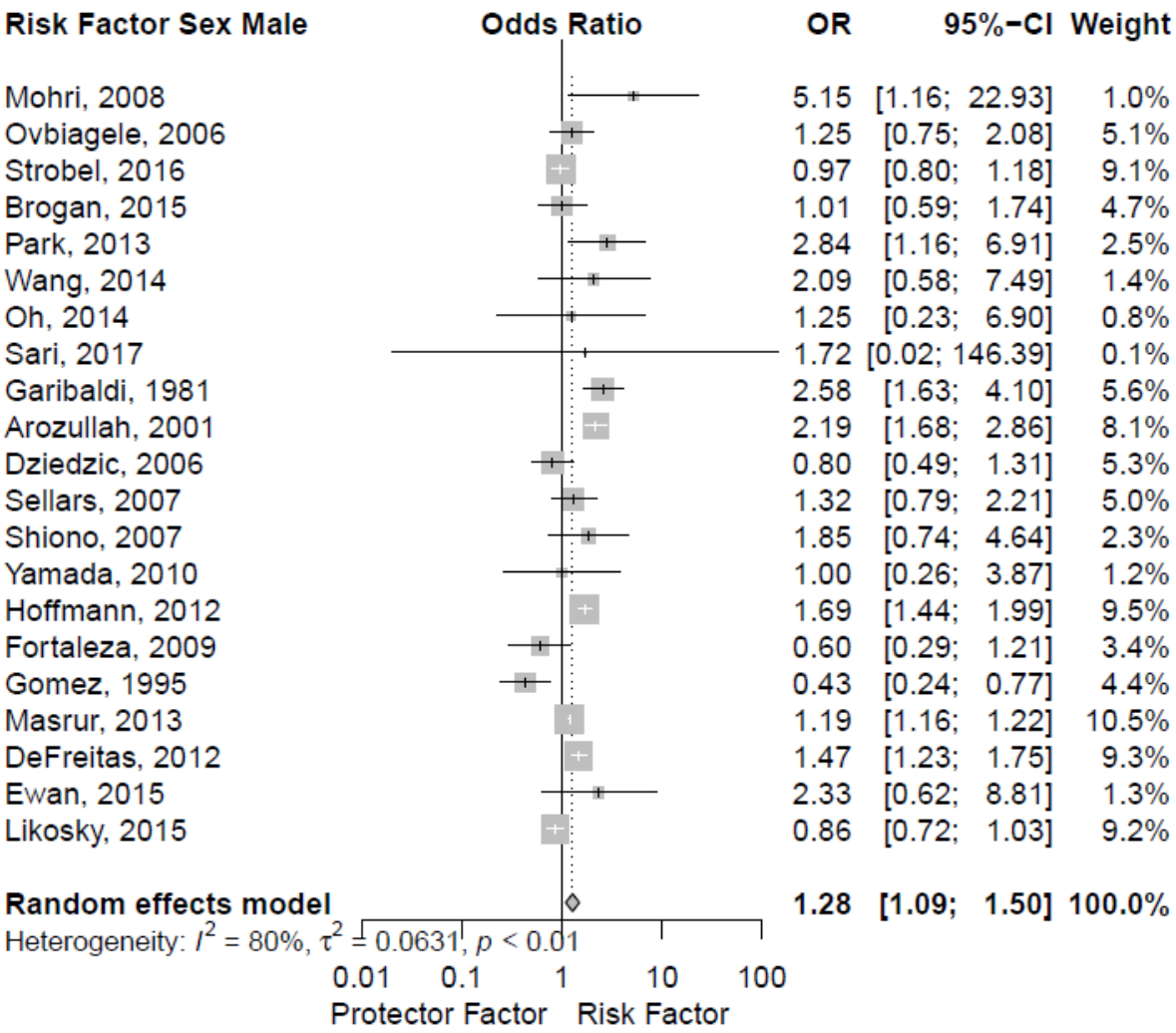


Figure 3. Forest plot of the metanalysis for gender male.The width of the horizontal line represents the 95% confidence interval (CI) of the individual studies, and the square represents the proportional weight of each study. Diamonds represent the pooled odds ratios (ORs) and 95% CI.

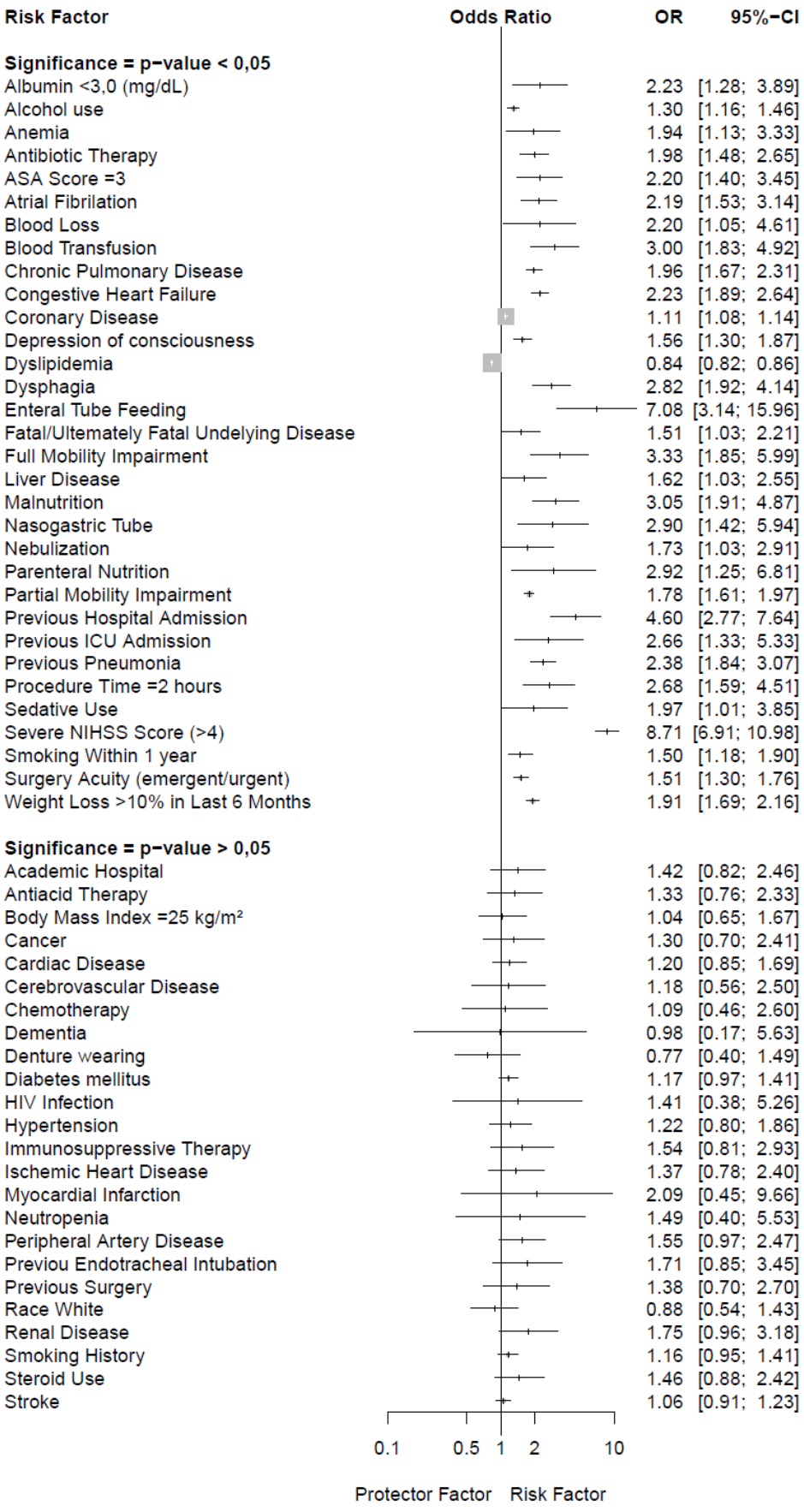


Figure 4. Forest plot of the metanalysis for the 56 predictor factors.The width of the horizontal line represents the 95% confidence interval (CI) of pooled odds ratio (ORs), and the square represents the pooled ORs.

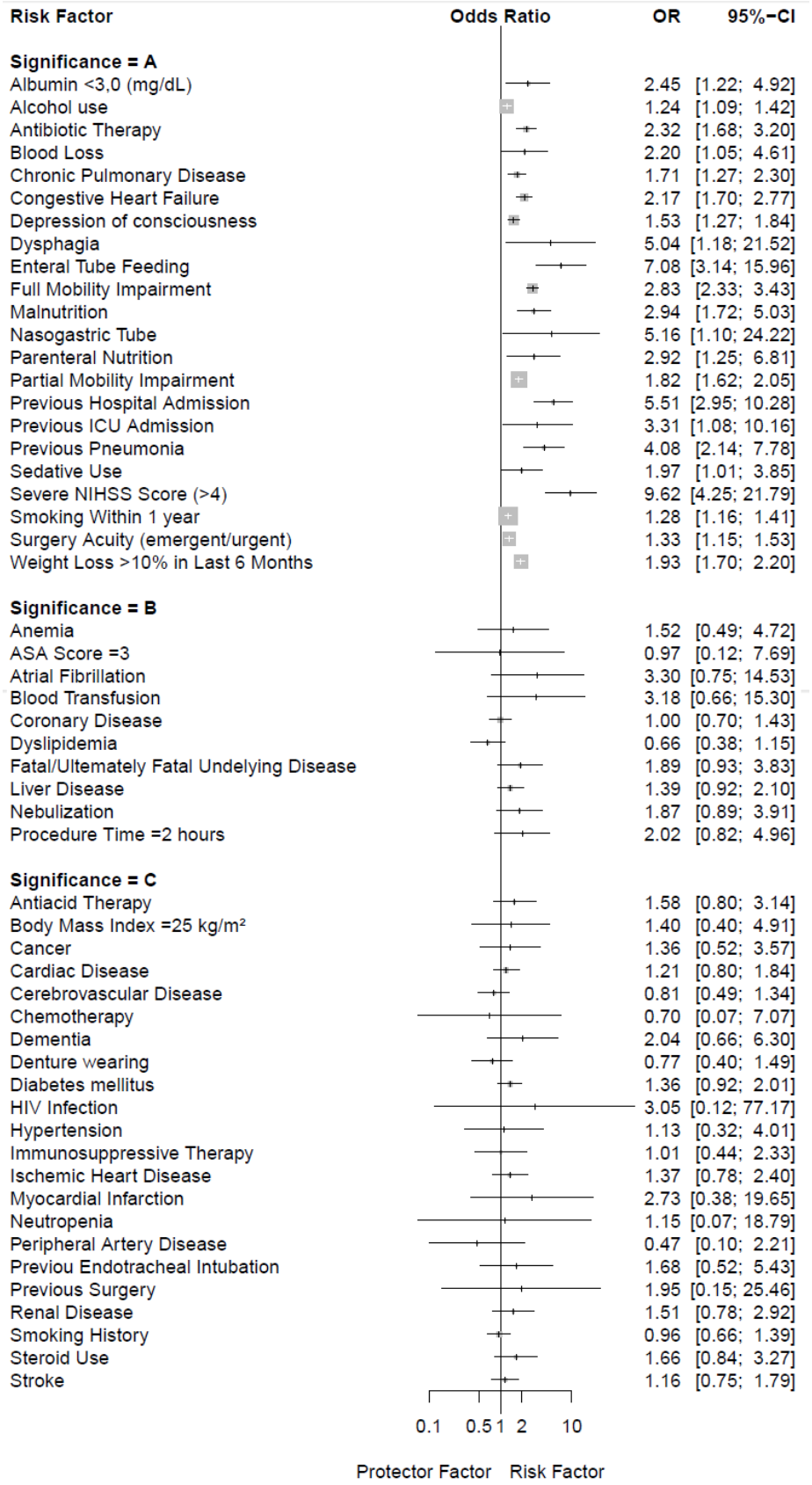


Figure 5. Sensibility analysis.The width of the horizontal line represents the 95% confidence interval (CI) of pooled odds ratio (ORs), and the square represents the pooled ORs. A=factors that remained significant after sensitivity analysis; B=factors that turned into non significant after sensitivity analysis; C=factors that remained non significant after sensitivity analysis.

Supplementary Table 1 – Risk of bias assessment in Cohort studies.

Criteria	Herzig, 2009	Bourdel-Marchasson, 2001	Burton, 2017	Ewan, 2015	Dziedzic, 2006	Ovbiagele, 2006
1. Was the research question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimated provided?	No	No	CD	Yes	No	No
6. For the analysis in this paper, were the exposure of interest measured prior to the outcome being measured?	NA	NA	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NA	NA	NA	NA	NA	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?	NA	Yes	CD	Yes	Yes	Yes
9. Were the exposure measures (independent variable) clearly defined, valid, reliable and implemented consistently across all study populations?	Yes	Yes	CD	Yes	Yes	No
10. Was the exposure (s) assessed more than once over time?	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	No
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	NR	NR	NR	NR	NR	NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?	Yes	No	CD	No	No	No
Quality Rating	GOOD	FAIR	FAIR	FAIR	FAIR	POOR

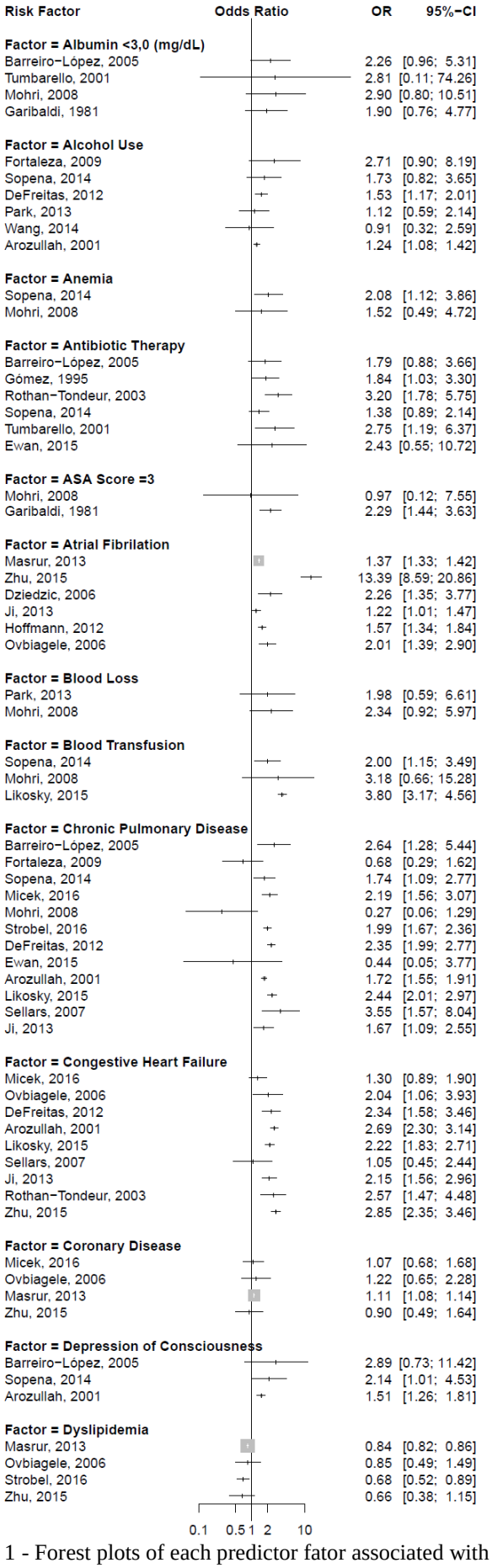
Criteria	Sellars, 2007	Chumbler, 2010	Hoffmann, 2012	Ji, 2013	Masrur, 2013	Brogan, 2015	Sari, 2016
1. Was the research question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimated provided?	Yes	No	No	No	No	No	No
6. For the analysis in this paper, were the exposure of interest measured prior to the outcome being measured?	NA	NA	NA	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NA	NA	NA	NA	NA	NA	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variable) clearly defined, valid, reliable and implemented consistently across all study populations?	Yes	Yes	Yes	Yes	Yes	No	Yes
10. Was the exposure (s) assessed more than once over time?	NA	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	No	No	Yes	No	No	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	NR	NR	NR	NR	NR	NR	NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?	No	No	Yes	Yes	Yes	No	No
Quality Rating	FAIR	POOR	POOR	GOOD	POOR	POOR	FAIR

Criteria	Likosky, 2015	Strobel, 2016	Mohri, 2008	Park, 2013	Garibaldi, 1981	Iwamoto, 1993	Arrozulah, 2001
1. Was the research question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimated provided?	No	No	No	No	No	No	No
6. For the analysis in this paper, were the exposure of interest measured prior to the outcome being measured?	NA	NA	NA	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NA	NA	NA	NA	NA	NA	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variable) clearly defined, valid, reliable and implemented consistently across all study populations?	No	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure (s) assessed more than once over time?	NA	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No	No	Yes	Yes	No	No	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	NR	NR	NR	NR	NR	NR	NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?	No	No	No	Yes	No	No	No
Quality Rating	POOR	POOR	FAIR	GOOD	POOR	POOR	FAIR

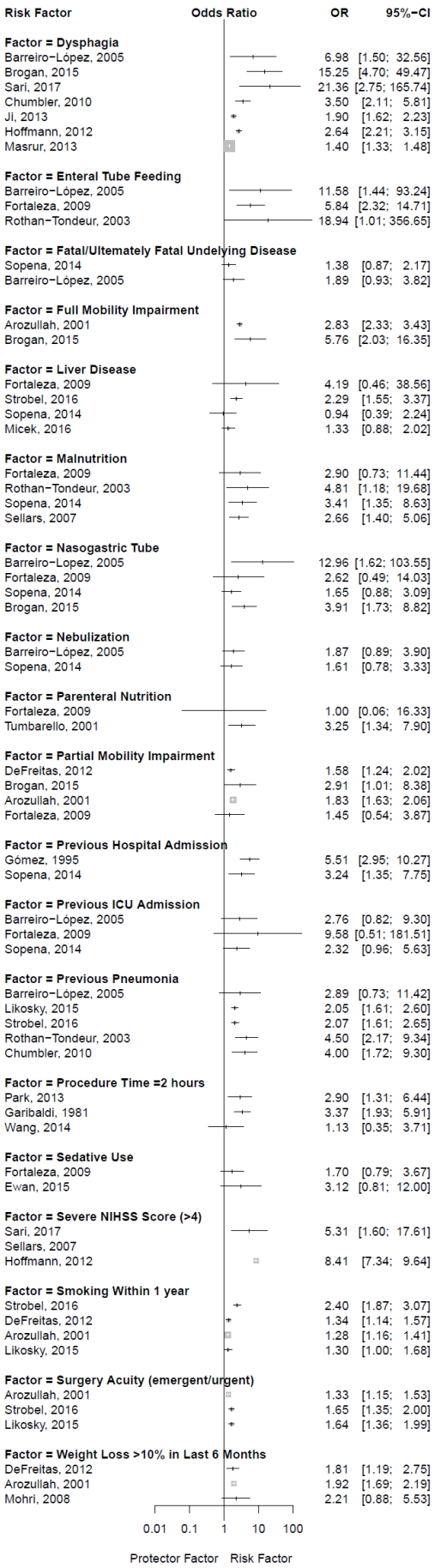
Criteria	Shiono, 2007	Yamada, 2010	Wang, 2014	Oh, 2014	DeFreitas, 2012	Zhu, 2015	Minakuchi, 2014
1. Was the research question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimated provided?	No	No	No	No	No	No	No
6. For the analysis in this paper, were the exposure of interest measured prior to the outcome being measured?	NA	NA	NA	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NA	NA	NA	NA	NA	NA	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?	Yes	NA	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variable) clearly defined, valid, reliable and implemented consistently across all study populations?	Yes	No	Yes	Yes	Yes	Yes	Yes
10. Was the exposure (s) assessed more than once over time?	NA	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No	No	Yes	No	No	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	NR	NR	NR	NR	NR	NR	NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?	Yes	Yes	No	No	Yes	Yes	No
Quality Rating	POOR	POOR	FAIR	POOR	POOR	GOOD	FAIR

Supplementary Table 2 – Risk of bias assessment in Case-Control studies.

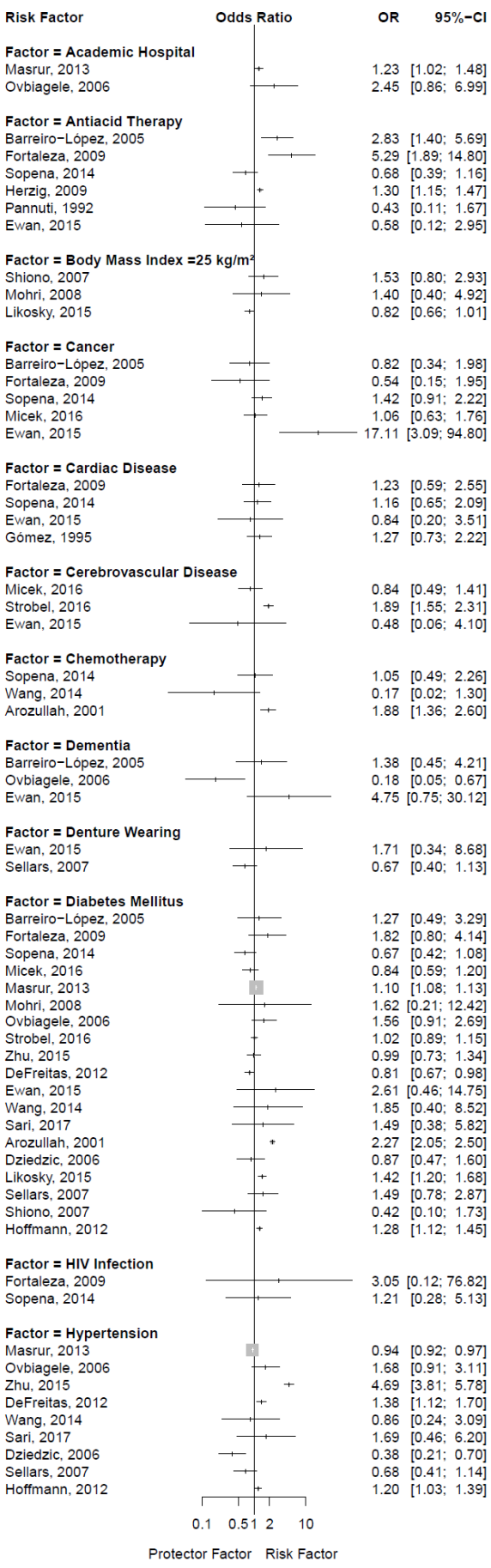
Criteria	Tumbarello, 2001	Sopena, 2014	Rothan-Tondeur, 2003	Pannuti, 1992	Micek, 2016	Gómez, 1995	Fortaleza, 2009	Barreiro-López, 2005
1. Was the research question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Did the authors include a sample size justification?	No	No	No	No	No	No	No	No
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identy or select cases and controls valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the cases clearly defined and differentiated from controls?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	CD	CD	Yes	Yes	Yes	CD	CD	CD
8. Was there use of concurrent controls?	No	No	No	No	No	No	Yes	No
9.Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	NA	NA	NA	NA	NA	NA	NA	NA
10. Were the measures of exposure/risk clearly defined, valid, reliable and implemented consistently (including same time period) across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	CD	CD	CD	CD	CD	CD	CD	CD
12. Were key potential confounding variables measured and adjusted in the analysis? If matching was used, did the investigators account for matching during study analysis?	No	No	No	No	No	No	No	No
Quality Rating	FAIR	POOR	FAIR	FAIR	FAIR	FAIR	FAIR	FAIR



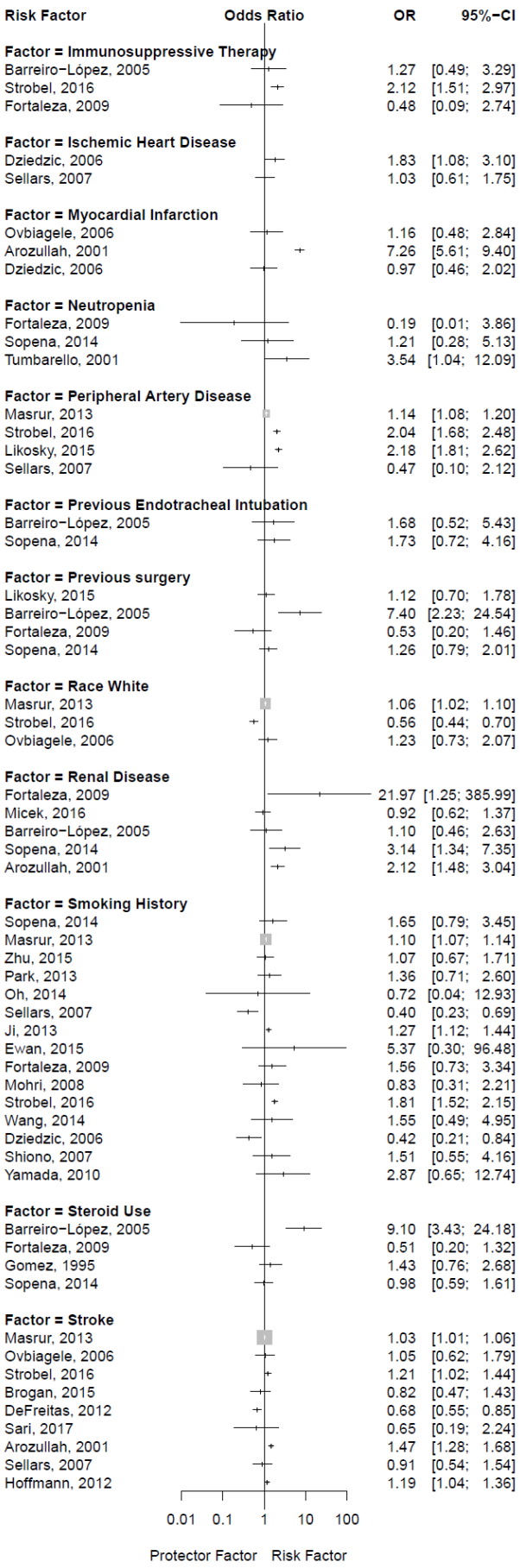
Supplementary Figure 1 - Forest plots of each predictor fator associated with NVHAP. [Continue]



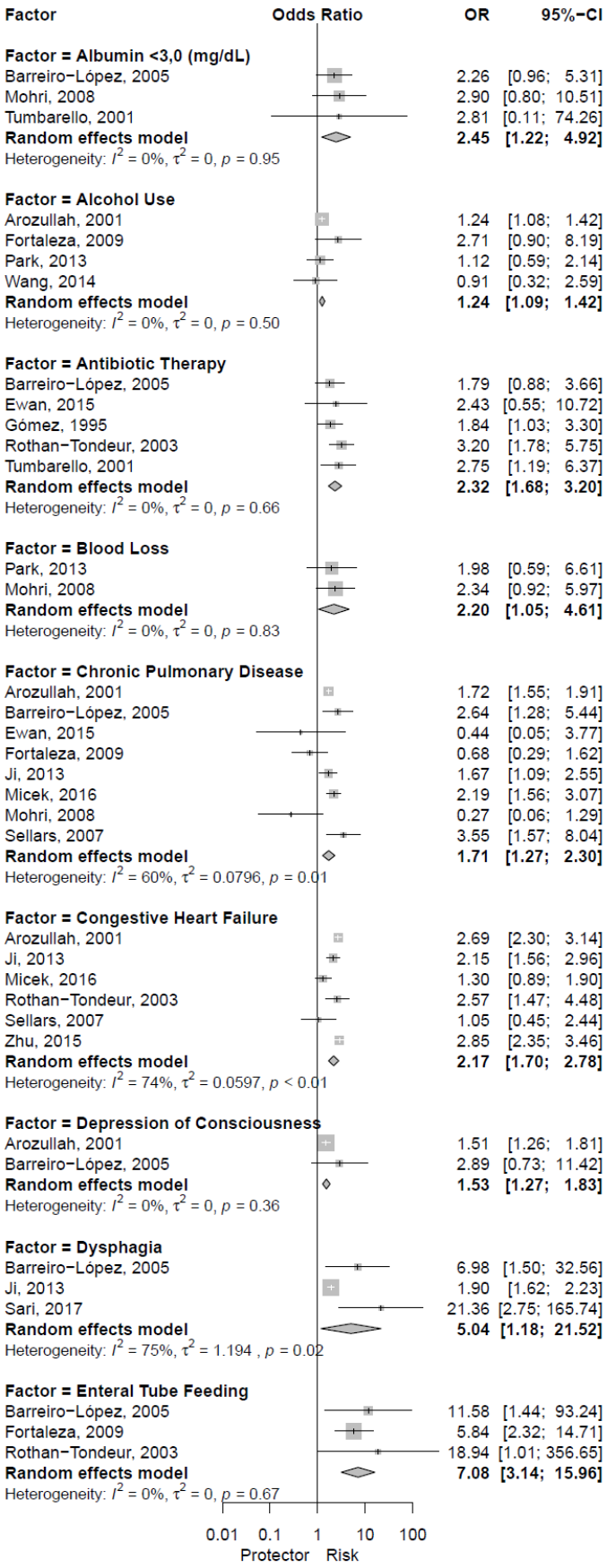
Supplementary Figure 1 - Forest plots of each predictor fator associated with NVHAP.



Supplementary Figure 2 - Forest plots of each predictor fator not associated with NVHAP. [Continue]

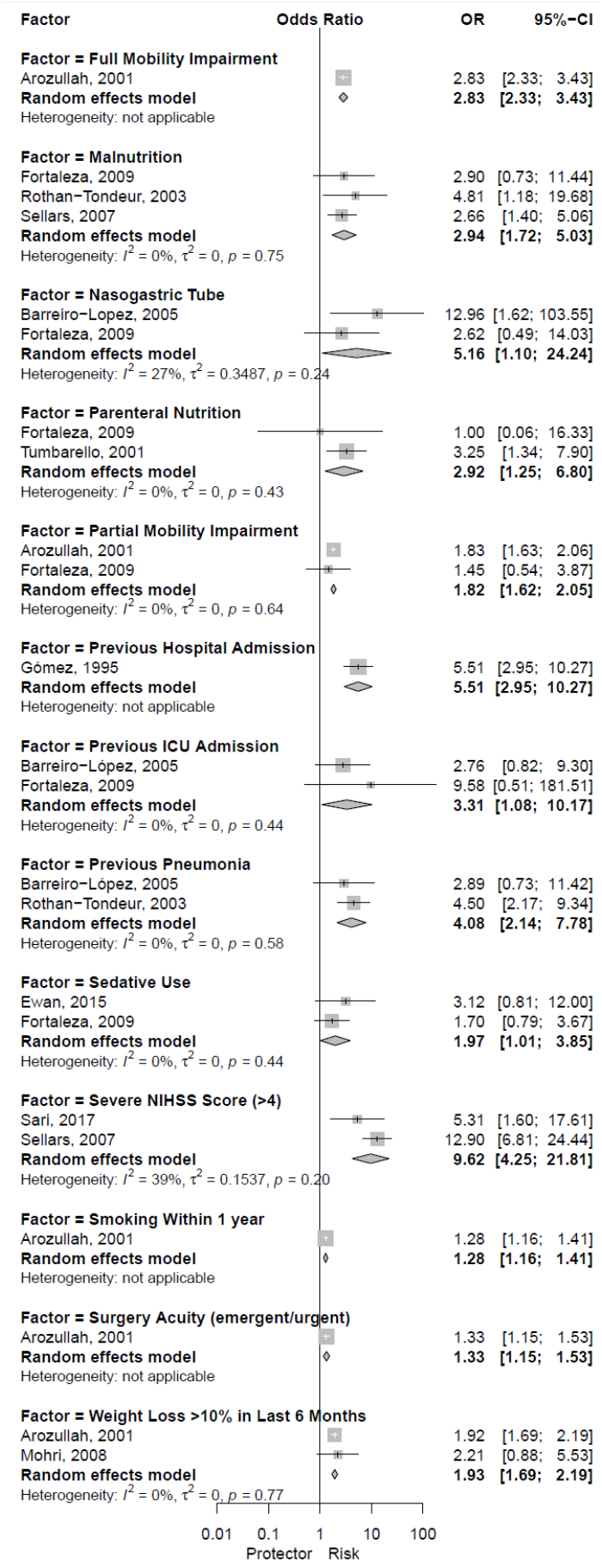


Supplementary Figure 2 - Forest plots of each predictor fator not associated with NVHAP.

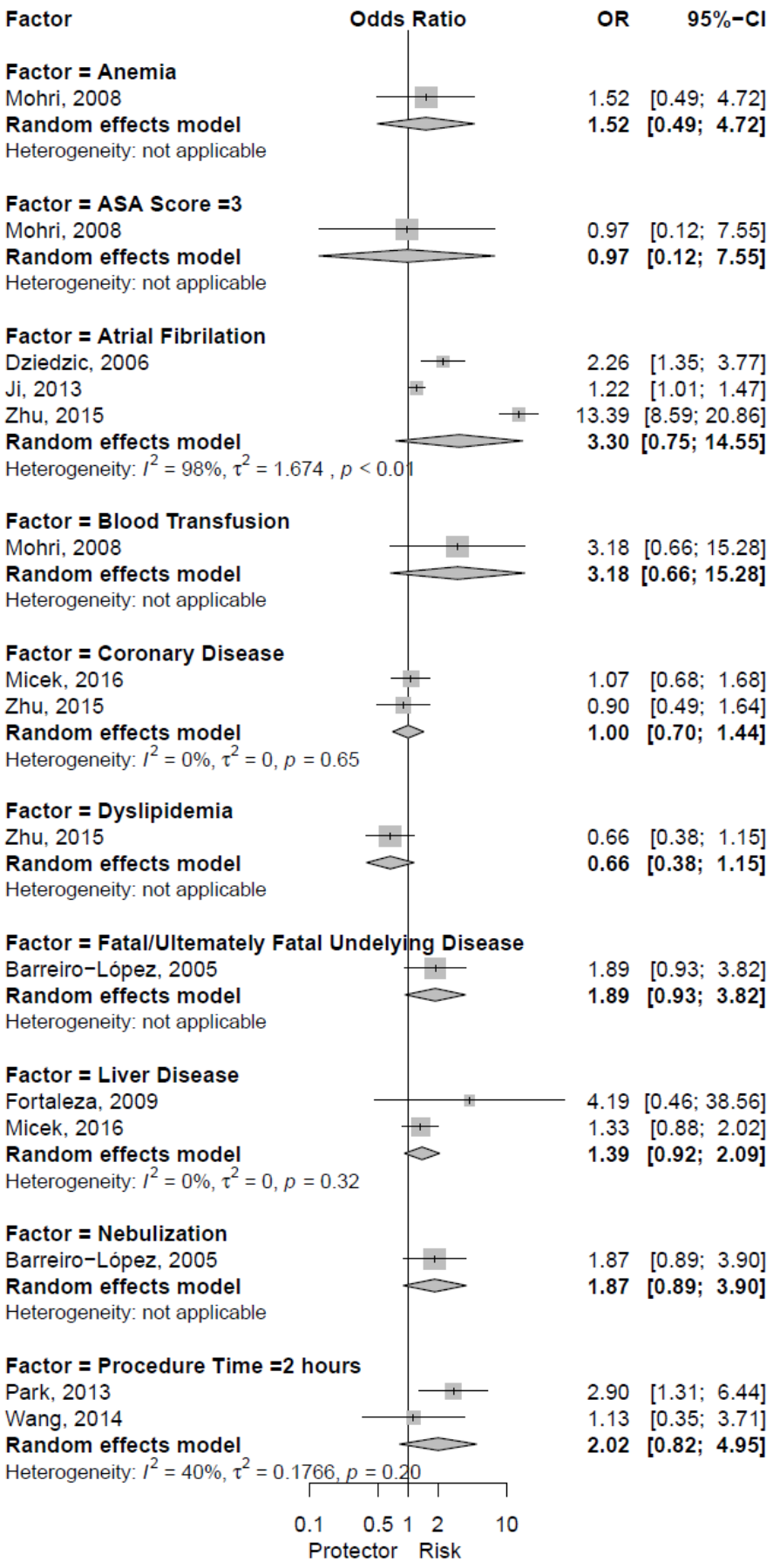


Supplementary Figure 3 – Risk factors that remained statistically significant after the sensitivity analysis.

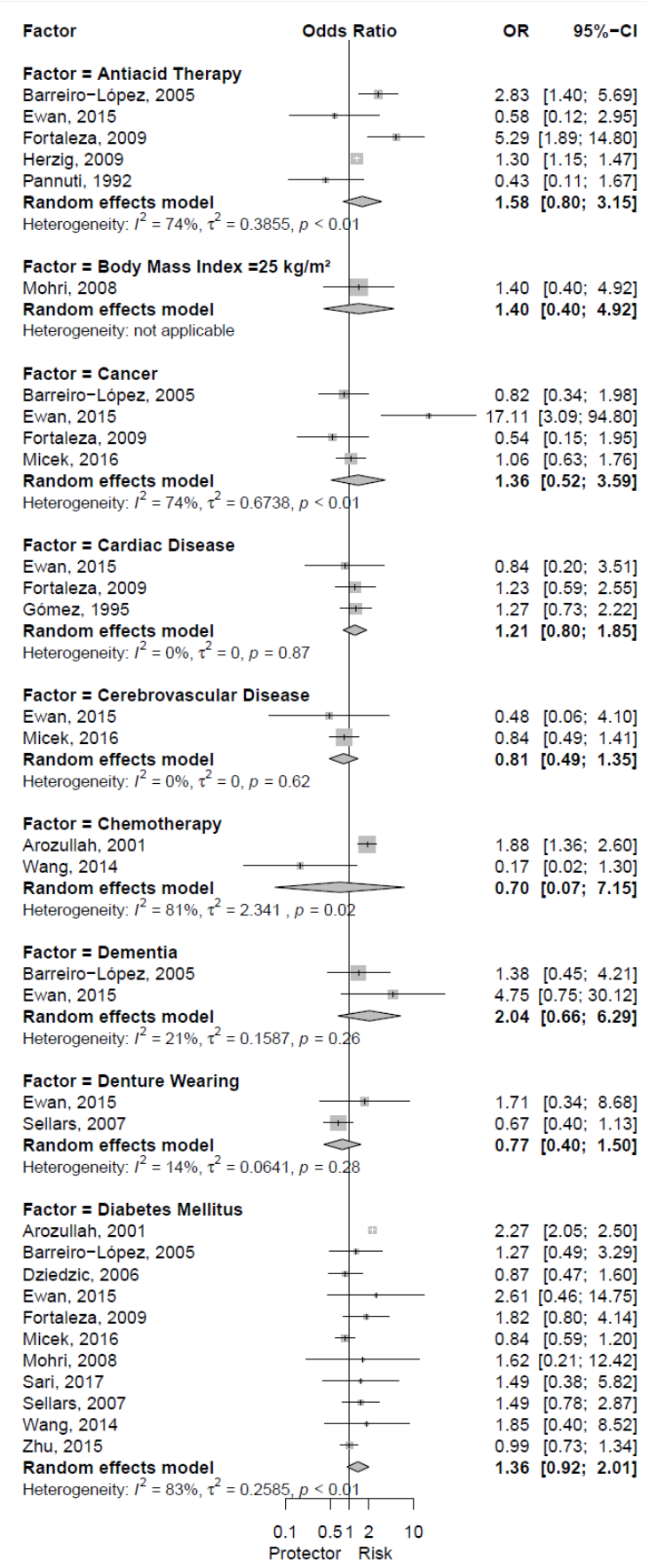
[Continue]



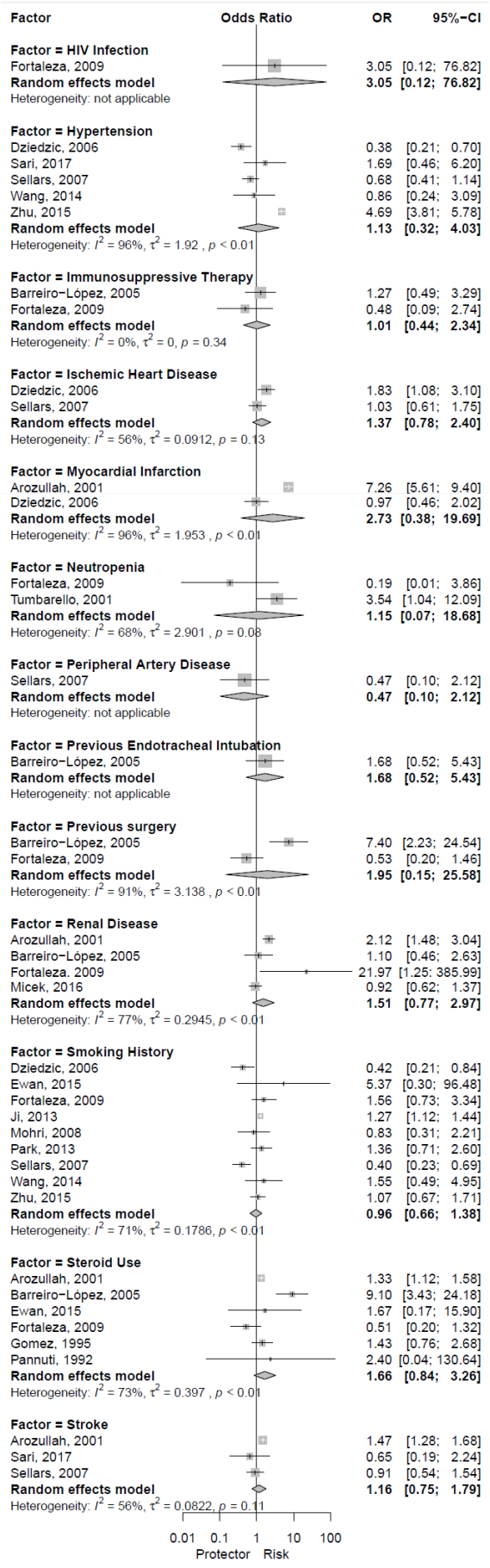
Supplementary Figure 3 – Risk factors that remained statistically significant after the sensitivity analysis.



Supplementary Figure 4 – Risk factors that became non-significant after the sensitivity analysis.



Supplementary Figure 5 – Non-significant risk factors before and after the sensitivity analysis. [Continue]



Supplementary Figure 5 – Non-significant risk factors before and after the sensitivity analysis.

8 CONCLUSÕES E CONSIDERAÇÕES FINAIS

As infecções hospitalares têm se mostrado cada vez mais prevalentes nas instituições de saúde, sendo consideradas eventos adversos graves relacionados à hospitalização. Entre as infecções respiratórias relacionadas à assistência hospitalar, as PAVM foram, e continuam sendo muito estudadas, especialmente no que tange ao estabelecimento de medidas para prevenção e controle, dada sua alta morbidade e mortalidade. No entanto, com o conhecimento das medidas para prevenir as PAVM suas taxas de incidência estão reduzindo e as PNVM ganharam maior importância, sendo atualmente responsáveis por cerca de dois terços do total de infecções respiratórias nas instituições de saúde.

Buscas na literatura mostraram que não há revisões de literatura avaliando a frequência da ocorrência e fatores relacionados às PNVM para que se possa determinar quantitativamente os fatores de risco e o impacto nos desfechos dos pacientes, assim como medidas para prevenção e controle. Dessa forma, esta revisão sistemática foi desenvolvida visando sistematizar os achados acerca dos fatores de risco para esta complicação infecciosa.

A busca sistemática na literatura científica retornou 35 estudos observacionais que foram desenvolvidos visando encontrar os fatores de risco para PNVM. Foram encontrados 269 fatores diferentes para o desenvolvimento de PNVM, sendo que 58 puderam ser incluídos em uma metanálise que definiu 22 fatores de risco como significativamente associados à PNVM. Além disso, este estudo identificou que a baixa qualidade dos estudos observacionais acerca da temática é importante. As falhas na definição do desfecho, demonstram haver necessidade de que novos estudos bem delineados sejam desenvolvidos para estabelecer definitivamente fatores de risco para PNVM. Definições claras e objetivas para o diagnóstico de PNVM são fundamentais para se evitar viés na seleção dos pacientes, o que limita a validade dos achados do estudo.

Em resumo, esta revisão sistemática atendeu aos objetivos propostos estabelecendo os fatores de risco para PNVM. Os achados desta pesquisa poderão contribuir para que estudos futuros possam ser desenvolvidos visando estabelecer os fatores de risco que deverão ser incluídos em modelos de *bundles* visando a redução desta importante infecção nas instituições de saúde.

ANEXO 1 – Instrumento de Avaliação da Qualidade Metodológica para Estudos de Coorte do *National Institute of Health*

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the

example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S.

consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of

participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study–in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other).

Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

ANEXO 2 – Instrumento de Avaliação da Qualidade Metodológica para Estudos Caso-Controle do *National Institute of Health*

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?			
2. Was the study population clearly specified and defined?			
3. Did the authors include a sample size justification?			
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
6. Were the cases clearly defined and differentiated from controls?			
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?			
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?			
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 Initials:
Rater #2 Initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Case-Control Studies

The guidance document below is organized by question number from the tool for quality assessment of case-control studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. High quality scientific research explicitly defines a research question.

Question 2. Study population

Did the authors describe the group of individuals from which the cases and controls were selected or recruited, while using demographics, location, and time period? If the investigators conducted this study again, would they know exactly who to recruit, from where, and from what time period?

Investigators identify case-control study populations by location, time period, and inclusion criteria for cases (individuals with the disease, condition, or problem) and controls (individuals without the disease, condition, or problem). For example, the population for a study of lung cancer and chemical exposure would be all incident cases of lung cancer diagnosed in patients ages 35 to 79, from January 1, 2003 to December 31, 2008, living in Texas during that entire time period, as well as controls without lung cancer recruited from the same population during the same time period. The population is clearly described as: (1) who (men and women ages 35 to 79 with (cases) and without (controls) incident lung cancer); (2) where (living in Texas); and (3) when (between January 1, 2003 and December 31, 2008).

Other studies may use disease registries or data from cohort studies to identify cases. In these cases, the populations are individuals who live in the area covered by the disease registry or included in a cohort study (i.e., nested case-control or case-cohort). For example, a study of the relationship between vitamin D intake and myocardial infarction might use patients identified via the GRACE registry, a database of heart attack patients.

NHLBI staff encouraged reviewers to examine prior papers on methods (listed in the reference list) to make this assessment, if necessary.

Question 3. Target population and case representation

In order for a study to truly address the research question, the target population–the population from which the study population is drawn and to which study results are believed to apply–should be carefully defined. Some authors may compare characteristics of the study cases to characteristics of cases in the target population, either in text or in a table. When study cases are shown to be representative of cases in the appropriate target population, it increases the likelihood that the study was well-designed per the research question.

However, because these statistics are frequently difficult or impossible to measure, publications should not be penalized if case representation is not shown. For most papers, the response to question 3 will be "NR."

Those subquestions are combined because the answer to the second subquestion–case representation–determines the response to this item. However, it cannot be determined without considering the response to the first subquestion. For example, if the answer to the first subquestion is "yes," and the second, "CD," then the response for item 3 is "CD."

Question 4. Sample size justification

Did the authors discuss their reasons for selecting or recruiting the number of individuals included? Did they discuss the statistical power of the study and provide a sample size calculation to ensure that the study is adequately powered to detect an association (if one exists)? This question does not refer to a description of the manner in which different groups were included or excluded using the inclusion/exclusion criteria (e.g., "Final study size was 1,378 participants after exclusion of 461 patients with missing data" is not considered a sample size justification for the purposes of this question).

An article's methods section usually contains information on sample size and the size needed to detect differences in exposures and on statistical power.

Question 5. Groups recruited from the same population

To determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control was to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest, e.g., lung cancer) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls were recruited from hospitals in a given region. One may reasonably assume that controls in the catchment area for the hospitals, or those already in the hospitals for a different reason, would attend those hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If the controls were recruited or selected from a different region (e.g., a State other than Texas) or time period (e.g., 1991-2000), then the cases and controls were recruited from different populations, and the answer to this question would be "no."

The following example further explores selection of controls. In a study, eligible cases were men and women, ages 18 to 39, who were diagnosed with atherosclerosis at hospitals in Perth, Australia, between July 1, 2000 and December 31, 2007. Appropriate controls for these cases might be sampled using voter registration information for men and women ages 18 to 39, living in Perth (population-based controls); they also could be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are individuals who would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls were selected appropriately from the same source population as cases.

In a prospective case-control study, investigators may enroll individuals as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. At this same time, they may recruit or select controls from the population without the outcome of interest. One way to

identify or recruit cases is through a surveillance system. In turn, investigators can select controls from the population covered by that system. This is an example of population-based controls. Investigators also may identify and select cases from a cohort study population and identify controls from outcome-free individuals in the same cohort study. This is known as a nested case-control study.

Question 6. Inclusion and exclusion criteria prespecified and applied uniformly

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the groups involved? To answer this question, reviewers determined if the investigators developed I/E criteria prior to recruitment or selection of the study population and if they used the same underlying criteria for all groups. The investigators should have used the same selection criteria, except for study participants who had the disease or condition, which would be different for cases and controls by definition. Therefore, the investigators use the same age (or age range), gender, race, and other characteristics to select cases and controls. Information on this topic is usually found in a paper's section on the description of the study population.

Question 7. Case and control definitions

For this question, reviewers looked for descriptions of the validity of case and control definitions and processes or tools used to identify study participants as such. Was a specific description of "case" and "control" provided? Is there a discussion of the validity of the case and control definitions and the processes or tools used to identify study participants as such? They determined if the tools or methods were accurate, reliable, and objective. For example, cases might be identified as "adult patients admitted to a VA hospital from January 1, 2000 to December 31, 2009, with an ICD-9 discharge diagnosis code of acute myocardial infarction and at least one of the two confirmatory findings in their medical records: at least 2mm of ST elevation changes in two or more ECG leads and an elevated troponin level. Investigators might also use ICD-9 or CPT codes to identify patients. All cases should be identified using the same methods. Unless the distinction between cases and controls is accurate and reliable, investigators cannot use study results to draw valid conclusions.

Question 8. Random selection of study participants

If a case-control study did not use 100 percent of eligible cases and/or controls (e.g., not all disease-free participants were included as controls), did the authors indicate that random sampling was used to select controls? When it is possible to identify the source population fairly explicitly (e.g., in a nested case-control study, or in a registry-based study), then random sampling of controls is preferred. When investigators used consecutive sampling, which is frequently done for cases in prospective studies, then study participants are not considered randomly selected. In this case, the reviewers would answer "no" to Question 8. However, this would not be considered a fatal flaw.

If investigators included all eligible cases and controls as study participants, then reviewers marked "NA" in the tool. If 100 percent of cases were included (e.g., NA for cases) but only 50 percent of eligible

controls, then the response would be "yes" if the controls were randomly selected, and "no" if they were not. If this cannot be determined, the appropriate response is "CD."

Question 9. Concurrent controls

A concurrent control is a control selected at the time another person became a case, usually on the same day. This means that one or more controls are recruited or selected from the population without the outcome of interest at the time a case is diagnosed. Investigators can use this method in both prospective case-control studies and retrospective case-control studies. For example, in a retrospective study of adenocarcinoma of the colon using data from hospital records, if hospital records indicate that Person A was diagnosed with adenocarcinoma of the colon on June 22, 2002, then investigators would select one or more controls from the population of patients without adenocarcinoma of the colon on that same day. This assumes they conducted the study retrospectively, using data from hospital records. The investigators could have also conducted this study using patient records from a cohort study, in which case it would be a nested case-control study.

Investigators can use concurrent controls in the presence or absence of matching and vice versa. A study that uses matching does not necessarily mean that concurrent controls were used.

Question 10. Exposure assessed prior to outcome measurement

Investigators first determine case or control status (based on presence or absence of outcome of interest), and then assess exposure history of the case or control; therefore, reviewers ascertained that the exposure preceded the outcome. For example, if the investigators used tissue samples to determine exposure, did they collect them from patients prior to their diagnosis? If hospital records were used, did investigators verify that the date a patient was exposed (e.g., received medication for atherosclerosis) occurred prior to the date they became a case (e.g., was diagnosed with type 2 diabetes)? For an association between an exposure and an outcome to be considered causal, the exposure must have occurred prior to the outcome.

Question 11. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This is important, as it influences confidence in the reported exposures. Equally important is whether the exposures were assessed in the same manner within groups and between groups. This question pertains to bias resulting from exposure misclassification (i.e., exposure ascertainment).

For example, a retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content because participants' retrospective recall of dietary salt intake may be inaccurate and result in misclassification of exposure status. Similarly, BP results from practices that use an established protocol for measuring BP would be considered more valid and reliable than results from practices that did not use standard protocols. A protocol may include using trained BP assessors, standardized equipment (e.g., the same BP device which

has been tested and calibrated), and a standardized procedure (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged).

Question 12. Blinding of exposure assessors

Blinding or masking means that outcome assessors did not know whether participants were exposed or unexposed. To answer this question, reviewers examined articles for evidence that the outcome assessor(s) was masked to the exposure status of the research participants. An outcome assessor, for example, may examine medical records to determine the outcomes that occurred in the exposed and comparison groups. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status. A reviewer would note such a finding in the comments section of the assessment tool.

One way to ensure good blinding of exposure assessment is to have a separate committee, whose members have no information about the study participants' status as cases or controls, review research participants' records. To help answer the question above, reviewers determined if it was likely that the outcome assessor knew whether the study participant was a case or control. If it was unlikely, then the reviewers marked "no" to Question 12. Outcome assessors who used medical records to assess exposure should not have been directly involved in the study participants' care, since they probably would have known about their patients' conditions. If the medical records contained information on the patient's condition that identified him/her as a case (which is likely), that information would have had to be removed before the exposure assessors reviewed the records.

If blinding was not possible, which sometimes happens, the reviewers marked "NA" in the assessment tool and explained the potential for bias.

Question 13. Statistical analysis

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Investigators often use logistic regression or other regression methods to account for the influence of variables not of interest.

This is a key issue in case-controlled studies; statistical analyses need to control for potential confounders, in contrast to RCTs in which the randomization process controls for potential confounders. In the analysis, investigators need to control for all key factors that may be associated with both the exposure of interest and the outcome and are not of interest to the research question.

A study of the relationship between smoking and CVD events illustrates this point. Such a study needs to control for age, gender, and body weight; all are associated with smoking and CVD events. Well-done case-control studies control for multiple potential confounders.

Matching is a technique used to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, an investigator might identify cases that have had a heart attack or stroke and then select controls of similar age, gender, and body weight to the cases. For case-control

studies, it is important that if matching was performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) should be controlled for in the analysis.

General Guidance for Determining the Overall Quality Rating of Case-Controlled Studies

NHLBI designed the questions in the assessment tool to help reviewers focus on the key concepts for evaluating a study's internal validity, not to use as a list from which to add up items to judge a study's quality.

Internal validity for case-control studies is the extent to which the associations between disease and exposure reported in the study can truly be attributed to the exposure being evaluated rather than to flaws in the design or conduct of the study. In other words, what is ability of the study to draw associative conclusions about the effects of the exposures on outcomes? Any such flaws can increase the risk of bias.

In critical appraising a study, the following factors need to be considered: risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues addressed in the questions above. High risk of bias translates to a poor quality rating; low risk of bias translates to a good quality rating. Again, the greater the risk of bias, the lower the quality rating of the study.

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the outcome and the exposure, the higher the quality of the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

If a study has a "fatal flaw," then risk of bias is significant; therefore, the study is deemed to be of poor quality. An example of a fatal flaw in case-control studies is a lack of a consistent standard process used to identify cases and controls.

Generally, when reviewers evaluated a study, they did not see a "fatal flaw," but instead found some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, reviewers examined the potential for bias in the study. For any box checked "no," reviewers asked, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, did this factor lead to doubt about the results reported in the study or the ability of the study to accurately assess an association between exposure and outcome?

By examining questions in the assessment tool, reviewers were best able to assess the potential for bias in a study. Specific rules were not useful, as each study had specific nuances. In addition, being familiar with the key concepts helped reviewers assess the studies. Examples of studies rated good, fair, and poor were useful, yet each study had to be assessed on its own.

APÊNDICE 1 – Estratégia de Busca da Revisão Sistemática

Estratégia de busca aplicada no PubMed:

(((nosocomial infection OR nosocomial infection [tw] OR cross infection [mh] OR hospital infection* OR healthcare associated infection* OR health care associated infection* OR Health-care associated infection*)) AND (pneumonia OR pneumonia [mh] OR pneumonia [tw] OR acquired pneumonia OR acquired pneumonia [tw] OR associated pneumonia [tw] OR associated pneumonia OR nosocomial pneumonia [tw] OR hospital acquired pneumonia OR healthcare associated pneumonia OR health care associated pneumonia OR health-care associated pneumonia OR respiratory tract infections [mh] OR respiratory tract infection [tw])) AND (risk factors [mh] OR risk factors [tw] OR risk factors [all fields] OR factor [tw] OR factors [tw] OR factor [all fields] OR factors [all fields] OR associated factors [tw] OR associated factors [all fields] OR associated factor [all fields] OR associated factor [tw] OR predictor [tw] OR predictor factor [tw] OR relative risk*)

Estratégia de busca aplicada no Embase:

#1 'risk factor'/exp

#2 (relative NEAR/3 risk*):ab,ti

#3 ‘relative risk’:ab,ti

#4 (risk NEAR/3 factor*):ab,ti

#5 ‘risk factors’:ab,ti

#6 'relative risk'

#7 (associated NEAR/3 factor*):ab,ti

8 ‘associated factor’

#9 'pneumonia'/exp

#10 pneumon*:ab,ti OR pleuropneumon*:ab,ti OR bronchopneumon*:ab,ti OR bronchit*:ab,ti OR tracheobronchit*:ab,ti

#11 'respiratory tract infection'/exp

#12 ’respiratory tract infection’/de OR ’lower respiratory tract infection’/de OR ’lung infection’/de OR ’chest infection’/de

#13 (respiratory NEAR/3 infect*):ab,ti

#14 'hospital infection'/exp

#15 'healthcare associated infection'/exp

#16 ’hospital infection’/de OR ’healthcare associated infection’/de

#17 ’cross infection’/de
#18 ’cross infection’:ab,ti
#19 (infection* NEAR/3 (hospital* OR nosocomial OR healthcare*)):ab,ti
#20 ((hospital* OR 'health care' OR healthcare* OR 'health-care' OR nosocomial*) NEAR/3 (acquired OR associat*)):ab,ti
#21 ‘hospital acquired pneumonia’/de
22 ‘nosocomial pneumonia’
#23 hap:ab,ti

Estratégia de busca aplicada no Lilacs:

(tw:pneumonia OR tw:hospital pneumonia OR tw:hospital acquired pneumonia OR tw:health care associated pneumonia OR tw:nosocomial pneumonia) AND (tw:risk factor OR associated factor OR relative risk)

Estratégia de busca aplicada no Scopus:

(‘risk factor’ OR risk factor OR ‘risk factors’ OR ‘associated factor’ OR associated factor OR ‘predictor factor’ OR ‘relative risk’) AND (pneumonia OR ‘hospital acquired pneumonia’ OR ‘healthcare associated pneumonia’ OR ‘health care associated pneumonia’ OR ‘health-care associated pneumonia’) OR (healthcare W/3 pneumonia) OR (health care W/3 pneumonia) OR (health-care W/3 pneumonia) OR (hospital W/3 pneumonia) AND (hospital W/3 infection) OR (healthcare W/3 infection)

APÊNDICE 2 – Protocolo publicado no PROSPERO

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 **Review title**
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Predictor factors for non-ventilated hospital-acquired pneumonia: a systematic review

2 **Original language title**
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 **Anticipated or actual start date**
Give the date when the systematic review commenced, or is expected to commence.
29/03/2017

4 **Anticipated completion date**
Give the date by which the review is expected to be completed.
31/03/2018

5 **Stage of review at time of this submission**
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 **Named contact**
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Stephani Amanda Lukasewicz Ferreira

7 **Named contact email**
Enter the electronic mail address of the named contact.
stephani.luka@gmail.com

8 **Named contact address**
Enter the full postal address for the named contact.

9 **Named contact phone number**
Enter the telephone number for the named contact, including international dialing code.

10 **Organisational affiliation of the review**
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
Federal University of Rio Grande do Sul
Website address:

11 **Review team members and their organisational affiliations**
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Ms	Stephani Amanda	Lukasewicz Ferreira	Epidemiology Program, Federal University of Rio

			Grande do Sul.
Mrs	Patrícia	Klarmann Ziegelmann	Epidemiology Program, Federal University of Rio Grande do Sul
Mr	Ricardo	Souza Kuchenbecker	Epidemiology Program, Federal University of Rio Grande do Sul
Mrs	Caroline	Deutschendorf	
Ms	Camila	Hubner Dalmora	

12 **Funding sources/sponsors**
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
None.

13 **Conflicts of interest**
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 **Collaborators**
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 **Review question(s)**
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
What are the predictor factors for non-ventilated hospital-acquired pneumonia (NVHAP) in adult patients?

16 **Searches**
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
The search will be performed in the following electronic databases: MEDLINE, EMBASE, Scopus, LILACS, The Cochrane Database of Systematic Reviews and Centre for Reviews and Dissemination (CDR). The OpenGrey database will be searched for the grey literature. The Database of Abstracts of Reviews of Effects (DARE) will be searched for additional reviews. Reference lists of relevant systematic reviews and included articles will also be reviewed. Abstracts of recent conferences in the area will also be searched. Hand searching will be performed in the main journals of the area, such as: American Journal of Infection Control, Infection Control and Hospital Epidemiology, Clinical Infectious Disease, Journal of Hospital Infection, Lancet Infectious Disease. The search strategy will include only terms relating to or describing the exposure. No language or publication year restrictions will be applied. Non-English language studies will be translated if time permits. The searches will be re-run just before the final analyses and further studies retrieved for inclusion.

17 **URL to search strategy**
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 **Condition or domain being studied**
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Non-ventilated hospital-acquired pneumonia (NVHAP).

19 **Participants/population**
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
The inclusion criteria are: • Studies performed with the adult population. The definition for adult population will be that considered by the authors of the studies; • Diagnose of NVHAP defined according to the definition proposed by the Centers for Disease Control and Prevention; • Studies performed with patients hospitalized in a clinical/medical, surgical, trauma or intensive care unit with the diagnose of NVHAP. The exclusion criteria are: • Patients in use of mechanical ventilation; • Patients with the diagnose of ventilator-associated pneumonia; • Studies developed with patients with community-acquired pneumonia.

20 **Intervention(s), exposure(s)**
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

The predictor factors for the development of NVHAP that will be evaluated are: aspiration of gastric content; previous aspiration; supine position; enteral feeding; oral hygiene; stress bleeding prophylaxis; transfusion; glucose control; antimicrobial agents use; previous hospital admission; previous admission at the ICU; presence of chronic lung disease; endotracheal intubation; coma; surgical procedures involving the head, neck, thorax or upper abdomen; immobilization due to trauma or illness; age; gender; malnutrition; severe underlying conditions, such as chronic kidney failure, hypertension and anemia. Additional factors may also be found and included.

21 **Comparator(s)/control**

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Not applicable.

22 **Types of study to be included**

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Both prospective and retrospective cohort, case-control and cross-sectional studies will be included. Case series and case reports will be excluded from the review due to the high potential for bias in these study designs.

23 **Context**

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Hospital-acquired pneumonia (HAP) is a type of respiratory tract infection developing more than 48 hours after hospitalization and that is not present at the time of hospital admission. This is a serious complication affecting approximately 20% of the patients admitted to the hospital. Different mechanisms may contribute to the development of NVHAP, such as: conditions favoring the aspiration into the respiratory tract, factors that enhance colonization of the oropharynx and/or stomach by microorganisms, prolonged use of mechanical ventilation, exposure to contaminated respiratory devices and/or contact with contaminated or colonized hands and host factors. Since ventilator associated pneumonia is a major problem in ICUs with high mortality rates, most of the studies have been conducted in these patients. However, epidemiological data have shown to be different between patients acquiring ventilator associated pneumonia in the ICU and patients acquiring NVHAP, showing the importance of identifying NVHAP as a clinical distinct entity in terms of both etiology and management. The data available on the predictor and prognostic factors of patients acquiring NVHAP have shown to be scattered and grouping and analyzing this data together may help to identify the patients at most risk of developing such infection and that need measures to reduce and prevent this complication.

24 **Primary outcome(s)**

Give the most important outcomes.

Non-ventilated hospital acquired pneumonia.

Give information on timing and effect measures, as appropriate.

25 **Secondary outcomes**

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Time between hospital admission and the development of the NVHAP.

Give information on timing and effect measures, as appropriate.

26 **Data extraction (selection and coding)**

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

The titles and abstracts of articles identified from the search strategy will be reviewed independently by two reviewers (where SALF will review all studies, while CHD and CD will independently review 50% of the studies each) to identify potentially relevant articles. The full text of the selected articles will then be obtained and reviewed independently by the same three reviewers (SALF, CHD and CD) using a standardized form to assess suitability for inclusion in the final review against the criteria defined above. Disagreements between the reviewers will be resolved by consensus. The same strategy with the three reviewers (SALF, CHD and CD) will be used for data extraction using a standardized form created by the authors of this review. The following information will be extracted from the studies that meet the inclusion criteria: study characteristics (objectives, study design, hospital ward) and NVHAP predictors. For each predictor data regarding the measures of relative effect will be collected (OR, RR or HR). Disagreements in this phase will be resolved through consultation with a third reviewer (PKZ).

27 **Risk of bias (quality) assessment**

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two reviewers (SALF and PKZ) will conduct the risk of bias assessment using the National Institutes of

Health (NIH) Quality Assessment Tool for Observational Cohort studies and for Case-control studies. The reviewers will conduct the assessment independently, blinded to each other's judgments. In case of disagreements a third reviewer (RSK) will be called to make a final decision.

28 **Strategy for data synthesis**
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
A narrative synthesis of the findings from the included studies will be provided structured around predictor factors data. Tables with individual studies' findings regarding predictor factors will be provided. Meta-analysis will be performed for all predictors where results are available from more than one study. In studies where associations between predictor and NVHAP are presented through multiple sequentially-adjusted models, the effect estimate and 95% CIs from the most fully-adjusted model will be used in the meta-analysis. Meta-analysis will be performed using Meta R Package (https://CRAN.R-project.org/package=meta). Sensibility analysis and publication bias (funnel plot and Egger's regression test) are planned.

29 **Analysis of subgroups or subsets**
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
Analysis separated by hospital ward will be performed.

Review general information

30 **Type and method of review**
Select the type of review and the review method from the drop down list.
Systematic review
Infections and infestations

31 **Language**
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English
Will a summary/abstract be made available in English?
Yes

32 **Country**
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Brazil

33 **Other registration details**
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 **Reference and/or URL for published protocol**
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 **Dissemination plans**
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Publication at an infectious diseases medical journal.
Do you intend to publish the review on completion?
Yes

36 **Keywords**
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
infection control
Hospital-acquired Pneumonia
Risk Factors

37 **Details of any existing review of the same topic by the same authors**
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 **Current review status**
Review status should be updated when the review is completed and when it is published.
Ongoing

39 **Any additional information**
Provide any further information the review team consider relevant to the registration of the review.

40 **Details of final report/publication(s)**
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.