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Clinical instability on discharge and hospital readmissions in adult patients hospitalized with community-acquired pneumonia: a systematic review with meta-analysis

Anne-Marie Dols

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UNIVERSITE GRENOBLE ALPES
FACULTE DE MEDECINE DE GRENOBLE

Année : 2016

N°

**Clinical instability on discharge and hospital readmissions in adult patients
hospitalized with community-acquired pneumonia: a systematic review
with meta-analysis**

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DIPLOME D'ETAT

DOLS ANNE-MARIE

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MCU-MG : Maître de Conférences des Universités de Médecine Générale

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RESUME

Objectifs : Evaluer l'association entre l'instabilité clinique à la sortie et la réadmission chez des patients adultes hospitalisés pour pneumonie aigue communautaire.

Méthode : Nous avons réalisé une revue systématique avec méta-analyse de données agrégées. Les études originales ont été identifiées via les bases bibliographiques Medline® et Central® depuis leur date de création jusqu'au 15 février 2016. Les études éligibles incluaient au moins 30 patients adultes hospitalisés pour pneumonie. L'odds ratio commun a été estimé par modèle à effets aléatoires.

Résultats : Parmi les 874 références identifiées par notre stratégie de recherche, cinq études ont été incluses dans la méta-analyse totalisant 3575 individus. L'association entre instabilité clinique et réadmission était statistiquement significative (OR=1,39, intervalle de confiance à 95% de 1,01 à 1,92 ; $P=0,045$). Aucune hétérogénéité entre études n'a été constatée ($I^2=0,0\%$) malgré des définitions de l'instabilité clinique légèrement différentes. Ce résultat était robuste en analyse de sensibilité réalisée par « leave-one-out ». Les données à disposition ne permettaient pas de considérer séparément les réadmissions évitables.

Conclusion : Présenter au moins un critère d'instabilité clinique au moment de la sortie est associé à un risque accru de réadmission chez les patients adultes hospitalisés pour pneumonie aigue communautaire. Cependant, comme dans toute méta-analyse de données issues d'études observationnelles, un potentiel biais de confusion ne peut être écarté. Une méta-analyse de données individuelles permettrait de discuter de la pertinence des critères et de leur seuils à utiliser.

Mots clefs : pneumonie aigue communautaire, instabilité clinique, réadmission

ABSTRACT

Aims : To assess the association between clinical instability at discharge and readmission for hospitalized adult patients with community-acquired pneumonia.

Method : We performed a systematic review with meta-analysis of aggregated data. Primary studies were identified by searching Medline® and Central® databases from inception to February 15, 2016 and by screening references of potential eligible records. Eligible studies of all designs included at least 30 adult patients hospitalized for pneumonia. Pooled odds ratio was estimated by random effect model.

Results : Of the 874 records retrieved from our search process, five studies were included in the meta-analysis totaling 3575 participants. Association between clinical instability and readmission was statistically significant (OR=1.39, 95% confidence interval 1.01 to 1.92, $P=0.045$). No evidence of between studies heterogeneity ($I^2=0.0\%$) was found despite different clinical instability definitions. This result was robust in sensitivity analysis by leave-one-out method. Data at disposal did not allow us to consider avoidable readmission apart.

Conclusions: Presenting at least one criterion of clinical instability at discharge is associated with higher risk of readmission in adult patients hospitalized for community acquired pneumonia. However, as in any meta-analysis of data from observational studies, confounding effects cannot be discarded. A meta-analysis of individual participant data could allow the discussion of clinical stability best definition by considering each criterion relevance and threshold.

Keywords: community-acquired infections, pneumonia, clinical instability, readmission

INTRODUCTION

Pneumonia accounts for more than 1 million hospitalizations annually in European Union¹ and for 1.2 in United States². That represents, for the latter, the first cause of hospitalization for morbid condition³. Patients discharged alive have an important risk of being readmitted (7 to 20%)⁴ leading to higher risk of iatrogenic complications⁵ for involved patients, and significant burden for the health care system. In United States, index hospital stays for pneumonia are in second position in proportion of all rehospitalizations after stays for heart failure⁶.

If all readmissions are not of hospital competences, a part of them seems to be avoidable. Considering all hospital stays (not for pneumonia only), this situation accounts for more than one to five readmissions at 30 days after discharge⁷.

Because of this assumption about avoidability, readmission rates after a hospital stay for pneumonia are used as quality indicator by Center for Medicare and Medicaid Services (CMS). Hospitals with readmission rates judged as excessive undergo financial penalties since 2013⁸.

In order to help judging readiness for discharge for hospitalized patients with community-acquired pneumonia (CAP), Halm *et al.*⁹ proposed criteria to define clinical stability and assessed the association of unfulfilled criteria with bad outcomes. In their definition, a stable patient associated, during a 24 hours period, temperature $\leq 37.8^{\circ}\text{C}$, heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mmHg, arterial oxygen saturation $\geq 90\%$ or $\text{PO}_2 \geq 60$ mmHg on room air, ability to maintain oral intake and normal mental status. About 19% of their sample was discharged with at least one unstable factor.

The association between clinical instability and readmission was unclear. Their results showed an increase risk of readmission when at least two criteria were unfulfilled but were

inconclusive for one criterion. Also, each clinical stability criterion seemed to be of different importance in predicting adverse outcomes¹⁰.

In other few studies, results varied with different timing for outcome assessment (60 days versus 30 days) or different readmission type (all readmissions versus pneumonia-related). Such uncertainty in the literature is illustrated by slightly different recommendations between international guidelines.

In order to clarify the association of clinical instability and readmissions, we performed a systematic review with meta-analysis of aggregate data. The purpose was to precisely measure of association estimates, and to explore consistency of results among studies with samples from different population and with potential different definition for clinical instability.

Our primary objective was to characterize the size and significance of the association between clinical instability at discharge (at least one criterion of clinical instability present) and hospital readmissions after a hospital stay for CAP in adult patients. We aimed to explore such association separately for all readmission and for avoidable ones.

Our secondary objective was to identify potential differences in readmission risk by nature of clinical instability criteria present.

METHOD

The method used for this review complies with the Cochrane Handbook for systematic review version 5.1.0¹¹. The reporting is based on the MOOSE¹² (Meta-analysis Of Observational Studies in Epidemiology) and PRISMA¹³ (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statements.

Eligible criteria

Types of studies. Original studies of all design were eligible if at least 30 participants were enrolled.

Participants. Eligible studies included adult participants of all ethnicities and comorbidities hospitalized for CAP. No restriction was made based on years and countries of participant recruitment.

Exposure. Only studies assessing criteria for clinical stability at discharge were eligible.

Outcome. All hospital readmission were considered eligible with no restriction regarding timing of measurement or specific causes of readmission.

Language. For practical reason only studies published in English, Russian, Spanish or French were included. Potential eligible studies published in other language were listed apart.

Information source

Studies were identified using Medline® and Cochrane Central Register of Controlled Trials (CENTRAL®) from each database inception onwards. We also screened the reference lists of potential eligible articles and previously published reviews and meta-analysis for additional records.

Search strategy

As provided in detail in Appendix 1, our search strategy used standardized medical subject heading (MeSH) and keywords for pneumonia and hospital readmission. The search was performed on February 15, 2016. No filter was used.

Study selection

Two reviewers independently screened each title and abstract for potential eligibility. Interrater agreement assessed by Kappa statistic was 0.51, ranging from 0.20 to 0.76 for each eligibility criterion. Full text publications of references rated as “relevant” or “unsure” by at least one of the two reviewers were reviewed for final eligibility by one reviewer using a specific form available in Appendix 2.

Data collection process

For each eligible study, the same reviewer systematically collected data on sample characteristics, settings, methods and aggregate results (odds ratio and 2*2 tables) for the association between clinical instability at discharge and readmission, by using a specific data extraction form (Appendix 3). Studies with insufficient detail to assess the association of interest were excluded.

We planned to collect data regarding all versus avoidable readmissions as separate outcomes, but none of the eligible studies used the latter.

Risk of bias in individual studies

The same reviewer appraised the methodological quality of each included study using a grid adapted from the Quality in Prognosis Studies Tool (QUIPS tool)¹⁴ (Appendix 4).

Six domains were rated at “high”, “low” or “unclear” risk of bias: the study participation, study attrition, clinical instability measurement, readmission measurement, confounding, and

statistical analysis or reporting. Odds ratios (ORs) of the association between clinical instability and readmissions were considered correctly adjusted if taking into account comorbidities and pneumonia severity as confounders. Pneumonia severity could be estimated by Pneumonia Severity Index (PSI) or CURB 65 score^{15,16}.

We did not determine a priori domains of most importance to assess the overall risk of bias in each study. So we did not perform sensitivity analysis based on risk of bias assessment. Instead, we discussed quality assessment results and its potential impact on meta-analysis results.

Statistical analysis

For each primary study we retrieved adjusted OR assessing the association between clinical instability and all readmissions. If no measure of association was available, crude OR were computed by using 2*2 tables. We did the same for associations between each clinical instability criterion and readmissions.

Meta-analysis. ORs of the association between clinical instability and readmission were pooled with a Der Simonian and Laird's random effects model¹⁷. Not enough studies were available to reproduce it for each clinical instability criterion.

Investigation of heterogeneity. Between studies heterogeneity was evaluated with I^2 statistics which represents the percentage of total variation across studies due to heterogeneity rather than chance¹⁸.

Sensitivity analysis. Robustness of pooled OR was checked by removing each study one by one ("leave-on-out" method).

Reporting bias. A funnel plot and Egger test were used to assess risk of publication bias¹¹.

Statistical analyses were performed with Stata software version 14.0 (College Station, TX: StataCorp; 2015).

Quality of evidence.

The quality of evidence was rated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach¹¹.

RESULTS

Studies selection

As illustrated in the flow diagram provided in Figure 1, 909 records were identified by electronic search, and 15 additional records through references screening.

After duplicate removal, titles and abstracts of 874 records were screened for eligibility. Among them, 240 were identified as potentially relevant and their full texts were sought for final eligibility assessment. Of these, we were unable to retrieve full text of the 19 references listed in Appendix 5.

A total of 205 records were excluded because of eligibility criteria. Three records listed in Appendix 5, were not written in eligible language. Other 10 records were excluded because data on clinical instability at discharge and readmission were not reported in sufficient detail to explore the association of interest.

Overall, six records displayed data^{9,19-23} on the association between clinical instability criteria and readmission and were considered in this review. Two of them reported different results of interest from overlapping samples^{20,22}. Finally, five studies^{9,19,21-23} enrolling 3575 participants discharged alive were included in the meta-analysis.

Study characteristics

Table 1 provides characteristics of the five studies included.

Setting: Two studies were performed in North America, two in Spain, and the last one in Israel.

Study design. Two studies^{22,23} were prospective cohort according to the Cochrane criteria¹¹. The other three cohorts^{9,19,21} assessed clinical instability retrospectively, by reviewing medical chart.

Participants. Three studies^{9,21,22} used clinical signs and radiological new infiltrate at presentation as criteria for pneumonia (Appendix 6). Dagan *et al.*¹⁹ did not specify diagnostic criteria but used a final diagnostic of CAP in the discharge letter. Adamuz *et al.*²³ mentioned the prospective recruitment of all CAP patients admitted with no precision. Except for the study published in 2009 by Capelastegui *et al.*²², which excluded nursing home residents, none of the included studies specified exclusion criteria for patients with health care associated pneumonia as defined by American guidelines²⁴.

Exposure. To define clinical instability on discharge, all the authors considered the five criteria: systolic blood pressure, heart rate, respiratory rate, temperature and oxygenation. They used quasi similar threshold except for one study²² with lower temperature threshold (≥ 37.2 versus >37.8) and higher heart rate threshold (≥ 120 versus >100) than used in other studies. Other criteria such as “possibility to eat” status or mental status on discharge were not systematic. Three studies used both^{9,19,23}. One study did not use them²¹. One study did not assess mental status on discharge for patients able to eat or to receive oral medication²² (see Appendix 7).

Prevalence of clinical instability at discharge ranged from 7.4 to 36.8%.

Outcome. Four studies assessed readmissions in the 30 days after hospital discharge whereas Jasti *et al.*²¹ considered them in the 30 days after index-hospitalization admission.

Risk of bias assessment

As illustrated in Table 2, two studies^{9,21} raised concern about potential bias due to participation as using samples younger and with lower risk for short term mortality than eligible patients^{25,26}.

A risk of bias linked to clinical instability measure was rated as high for one study²³ whom missing data rate reached 6.9% of the all sample and differed regarding the fact of having health care interaction – including hospital readmission – or not. For another study, missing data for clinical instability accounted for 3% of the sample with no evidence for a link with readmission status²². This study was rated as unclear for the risk of bias due to clinical instability measurement. In three studies, some information was lacking regarding the method used for clinical instability measurement. Authors did not specified time period^{19,22}, the way of retrieving measures from medical chart^{19,21,22} or reasons for cut off threshold choice^{20,22}. However, this lack of information was considered not to impact risk of bias judgment.

Regarding the outcome of interest, we checked if authors were able to catch all readmissions, and notably the ones occurring in other hospitals than the one of initial stay. For one study the way of retrieving readmission was not specified preventing risk of bias judgment¹⁹. Another study²³ recorded the first episode of health care interaction including primary care visits, emergency department visits and readmission and was therefore at risk of missing hospital readmission events occurring after an episode of health care interaction.

Finally regarding confounders, three studies^{19,21,22} did not display measures of the association between clinical instability on discharge and all readmissions adjusted on pneumonia severity and comorbidities.

Association between clinical instability at discharge and readmission

Individual studies. Association between clinical instability at discharge and readmission was not statistically significant in any of the five individual studies included. ORs ranged from 0.56 to 1.76 (Figure 2). Two of them were adjusted for at least pneumonia severity and comorbidities^{9,23}. Others were crude ORs and one²² of them was computed by using an assumption on sample distribution based on study results (Appendix 8).

Meta-analysis. Pooled OR for the association between clinical instability on discharge and readmission was estimated at 1.39 with a 95% confidence interval (CI) from 1.01 to 1.92, with a p value of 0.045, indicating a higher risk of readmission for non-stable patients. There was no evidence of heterogeneity ($I^2=0.0\%$).

Egger test revealed no evidence for publication bias ($P=0.161$). The small number of studies makes funnel plot (Figure 3) difficult to interpret.

The direction and magnitude of pooled ORs did not change markedly after each individual study removal in sensitivity analysis (Table 3) arguing for robust results.

Quality of evidence. The quality of evidence supporting that clinical instability is associated with readmission with an OR closed to 1.4 is low.

Clinical instability criteria. Two records^{20,21} displayed data on the association between each clinical instability criterion and readmission, except for “mental status” and “ability to eat” criteria. Results were not statistically significant except for oxygen saturation on discharge in one study²⁰. Abnormal oxygen saturation was associated with higher risk of readmission at 30 days with adjusted hazard ratio at 1.8 and 95% CI (1.1-3.2).

DISCUSSION

With a pooled OR estimated at 1.39 (95% CI: 1.01-1.92), our analysis demonstrates that presenting at least one criterion of clinical instability in the last 24h of hospitalization is associated with higher risk of hospital readmission in adult patients hospitalized with CAP.

For practical implications, our findings emphasize the need for a close monitoring of temperature, respiratory rate, heart rate, blood pressure, oxygenation, mental status and ability to eat status. Also our results show that one abnormal criterion calls to delay a patient discharge or to adapt it. The need of clear statements for hospital discharge had been demonstrated in the literature.

Indeed, substantial between hospitals variability in length of stays for hospitalized CAP has been described in both North America and Europe^{27,28}, even after adjustment on pneumonia severity and complications during hospital stay. As explained by authors, such variability could be due to hospital organizations for a part, and clinicians practice for another part^{23,24}.

This last hypothesis has been tested in another study²⁹ assessing the way of how physicians make decision for discharging patients with CAP. Results showed that clinical factors identified as important in determining readiness to discharge varied substantially between physicians²⁹. Indeed, the study proposed to clinicians a list of 11 clinical factors to be rated as “very important”, “somewhat important” “no important” and “not relevant” in determining whether the patient was stable enough for discharge. The five most frequently factors identified as “very important” were only cited by between 42% (for “oxygenation returned to baseline”) and 66% (for “temperature returned to normal”) of clinicians²⁹. Another study on decision to switch from intravenous to oral antibiotic suggests that even using the same criteria for clinical stability, clinicians can refer to different threshold to define stability¹⁰.

If our results may help clinician decision, direct applicability asks for discussion.

First, the outcome used in this meta-analysis includes all hospital readmissions and therefore possibly planned procedures (such as hospital stay for surgery), which are not determined by suboptimal medical practice³⁰. Avoidable readmissions would have been more suitable to our goal. However, in addition of not being available in included individual studies, the approach used to define such concept varies a lot in the literature³¹ and remains not consensual.

Secondly, clinical instability definition was not exactly the same across included studies. To address such issue we aimed to analyze the association between each clinical instability criterion and readmission, and to test different way of pooling them to determine the most accurate definition for clinical instability at discharge. Unfortunately, no enough data were available to thoroughly do so. A meta-analysis of individual participant data could allow it and could test different thresholds for clinical instability criteria. Indeed, criteria and thresholds proposed by Halm *et al*⁹ were based on literature^{32,33} and physician experience³⁴. To our knowledge, the authors did not performed accuracy tests for different thresholds^{32,33}.

Finally, regarding the targeted patients with CAP, it is important to notice that hospitalized acquired pneumonias were well excluded from individual studies thanks to inclusion criteria. Whereas health care associated pneumonia as defined by American guidelines²⁴ were not, asking for precaution in results extrapolation.

This meta-analysis constitutes the first summary of evidences published on the association between clinical instability and readmission in CAP patients. Five original studies were included involving 3575 patients from 14 hospitals principally situated in Europe and North America. Our result was robust to sensitivity analysis. We found no evidence of between studies heterogeneity ($I^2=0.0\%$) despite slightly different clinical instability definitions. However this meta-analysis has several limitations that must be considered.

First, included studies revealed a high risk of bias in regards to our primary objective. In two studies^{9,21}, participants were different from eligible non-included patients by age and pneumonia severity score. However, the impact on meta-analysis results validity is not clear, notably because adjustment on potential confounders, as done in one study⁹, could have reduced it³⁵. For the remaining study²¹, a risk of bias due to confounders remains, as for two other studies^{19,22} for whom adjusted OR were not available. This limit is however inherent to any meta-analysis of aggregate data from observational studies^{36,37}.

One study²³ raised concern about risk of bias due to both clinical instability and readmission measurement. However after its removal in sensitivity analysis, estimated OR did not changed significantly in both magnitude and direction.

Secondly, we identified primary studies by an extensive literature search with no term for clinical instability concept in order not to be too restrictive. With this strategy, it seems unlikely that eligible published references could have been missed. However, we were unable to retrieve 19 records judged as possibly relevant in title and abstract screening, preventing us for testing final eligibility for them. Yet, none of their abstracts mentioned assessing clinical stability or other criteria for readiness to discharge. Among the five records³⁸⁻⁴² who aimed to analyze potential predictor of readmission in patient with pneumonia, two used administrative database^{38,39} and so could not retrieved clinical instability, two were published in 1995^{40,41} (before Halm *et al.* papers^{9,34}). Therefore the risk of having potential eligible studies in those 19 records seems very low.

Third, the small number of included studies call for precautions when considering statistical result for publication bias assessment¹¹.

Regarding the quality of evidence rating, we did not change initial grade allocated to meta-analysis of data from observational studies.

CONCLUSIONS

Despite some limitations, this systematic review suggests that adult patient hospitalized for CAP presenting at least one criterion for clinical instability on discharge has to be considered by clinicians at higher risk for hospital readmission.

More studies, notably meta-analysis on individual participants data, are however necessary for a better adjustment of confounding, and in order to discuss criteria and thresholds for clinical instability definition.

Instabilité clinique à la sortie et réadmissions hospitalières chez les patients adultes hospitalisés pour pneumonie aigue communautaire : une revue systématique de la littérature avec méta-analyse.

Thèse soutenue par Anne-Marie DOLS

CONCLUSION

La pneumonie est à l'origine de plus d'un million d'hospitalisations par an en Europe. Le taux de mortalité à 30 jours est de 10% à 12% et le taux de réadmission à 30 jours de 7% à 20%. Un peu plus d'une réadmission sur cinq serait évitable.

Des critères de stabilité clinique ont été proposés et ont fait l'objet de recommandations de pratique clinique pour guider la décision de sortie de patients hospitalisés pour pneumonie aigue communautaire. Ces critères comprennent : une température $\leq 37,8^{\circ}\text{C}$, un rythme cardiaque $\leq 100/\text{min}$, une fréquence respiratoire $\leq 24/\text{min}$, une pression artérielle systolique $\geq 90\text{mmHg}$, une saturation en oxygène $\geq 90\%$, la capacité à prendre un traitement oral et l'absence de confusion. Cependant, les données sur l'association de l'instabilité clinique avec le risque de réadmission sont parcellaires et contradictoires.

Nous avons réalisé la première revue systématique avec méta-analyse testant la valeur prédictive de l'instabilité clinique pour le risque de réadmission à 30 jours chez des patients adultes avec pneumonie aigue communautaire. Cinq études originales ont été identifiées totalisant 3.575 patients provenant de 14 hôpitaux situés principalement en Europe et en Amérique du Nord. Le taux de réadmission à 30 jours variait de 8% à 12% et la mortalité à 30 jours de 3% à 5%. Trois études ont utilisé les sept critères d'instabilité, deux n'en n'ont utilisé que cinq. L'une d'entre elles n'a pas évalué la confusion et la capacité à prendre un traitement oral. L'autre n'a pas évalué la confusion chez des patients sortant, capables de prendre un traitement oral. Une étude a utilisé des seuils différents de ceux préconisés. La prévalence de l'instabilité clinique à la sortie variait de 7% à 37%.

Dans un modèle à effets aléatoires, la présence d'au moins un critère d'instabilité clinique à la sortie était associée à un odds ratio de réadmission à 30 jours égal à 1,39 (intervalle de confiance à 95% de 1,01 à 1,92 ; $P=0,045$). Ce résultat était robuste en analyse de sensibilité réalisée par la méthode du « leave-one-out ». Nous n'avons pas mis en évidence d'hétérogénéité entre les études ($I^2=0,0\%$ et $P=0,65$), en dépit de définitions d'instabilité différentes. Le risque de biais, évalué à l'aide de l'outil « QUIPS », était élevé pour l'évaluation de l'instabilité et de la réadmission dans une étude. Il n'y avait pas d'argument en faveur d'un biais de publication ($P=0,16$), bien que l'effectif réduit d'étude incite à une interprétation prudente.

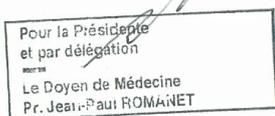
Les résultats de cette méta-analyse supportent les recommandations internationales préconisant l'évaluation de l'instabilité clinique à l'aide de critères formalisés dans les 24 heures précédant la sortie d'un patient hospitalisé avec une pneumonie aigue communautaire. (Niveau de preuve faible avec la grille GRADE).

Une méta-analyse sur données individuelles permettra d'identifier les critères éventuellement redondants (fréquence respiratoire et saturation en O_2 à l'oxymétrie de pouls).

VU ET PERMIS D'IMPRIMER

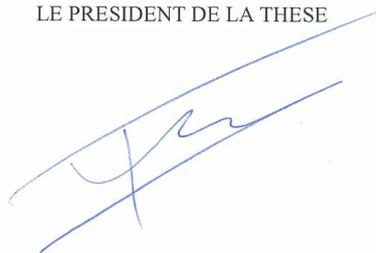
Grenoble, le 23/09/16

LE DOYEN



PROFESSEUR J.P. ROMANET

LE PRESIDENT DE LA THESE



PROFESSEUR P. FRANCOIS

TABLES AND FIGURES

Figure 1. Studies selection process

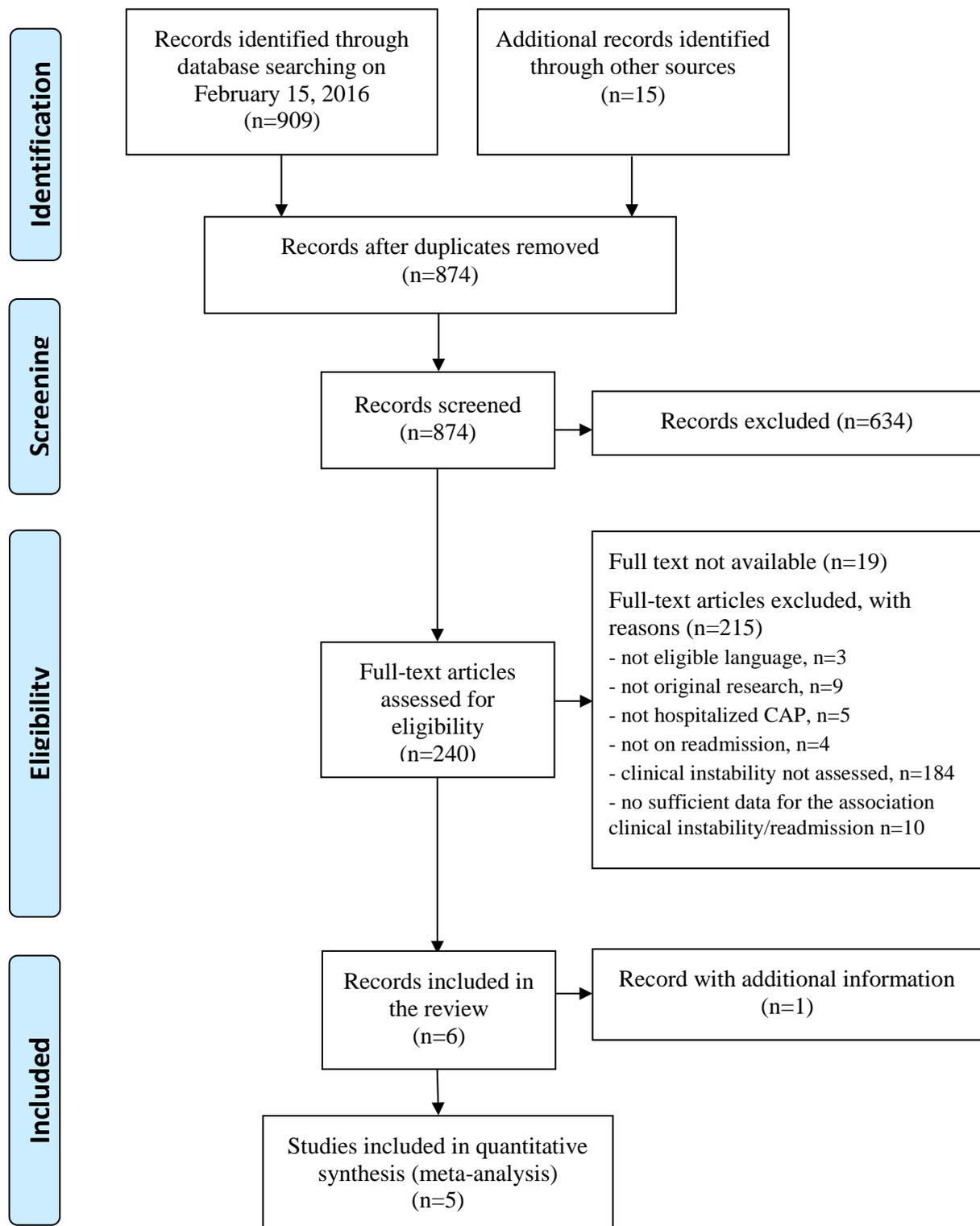


Table 1. Characteristics of included studies

Reference	Adamuz, 2011	Capelastegui, 2009	Dagan, 2006	Halm, 2002	Jasti, 2008
Country	Spain	Spain	Israel	USA Canada	USA
No of centers	1	1	1	4	7
Enrollment period	2007-2009	2003-2007	2002	1991-1994	1998-1999
Inhospital mortality, No (%)	106 (11.3)	72 (6.1)	NA	NA	27 (4.4)
Sample discharged alive	828	1117	373	680	577
High risk PSI classes, No (%)	515 (62.2)	543 (48.6)	206 (55.2)	194 (28.5)	268 (46.4)
Age, mean \pm SD	-	69.4 \pm 16.6	63.4 \pm 11.6	57.9 \pm 19.3	-
Male, No (%)	545 (65.8)	-	201 (53.9)	331 (48.7)	263 (45.6)
Median LOS	7	3	-	7	5
Clinical instability‡, No (%)	57 (7.4) [§]	399 (36.8) [§]	82 (22)	130 (19)	59 (10.2)
30 days mortality, No (%)	-	55 (4.9)	11 (2.9)	23 (3.4)	5 (4.2)
30 days readmission, No (%)	72 (8.7)	81 (7.2)	28 (7.5)	67 (9.9)	70 (12)

PSI: pneumonia severity index, SD: standard deviation, LOS: length of hospital stay

High risk PSI classes: classes IV and V

‡ number of patients with 1 or more instability criteria at discharge

§ Percentages exclude patients with missing data

Table 2. Risk of bias assessment

Reference	Study participation	Study attrition	Clinical instability measurement	Readmission measurement	Confounding	Analysis and reporting
Adamuz, 2011	+	+	-	-	+	+
Capelastegui, 2009	+	+	?	+	-	+
Dagan, 2006	+	+	+	?	-	+
Halm, 2002	-	+	+	+	+	+
Jasti, 2008	-	+	+	+	-	+

Low risk of bias reported as “+”, Unclear as “?”, High as “-”.

Study participation:

Halm and Jasti included patients younger and with less severe pneumonia (considering PSI) than eligible patients with participation rate of 40% and 55.5%.

Clinical instability measurement:

7 % of Adamuz sample has missing data regarding clinical instability, with missing data status depending on outcome. For Capelastegui, clinical stability measurement was missing for 3% of the sample with no information regarding differences by outcome.

Readmission measurement:

Adamuz *and al.* assessed the first episode of additional health-care within 30 days of discharge. Therefore hospitalizations stay after primary-care visit may not be assessed. Explanation about the way of assessing readmission is missing in Dagan’s paper, preventing us to evaluate if all readmission were well considered.

Confounding:

ORs for the association between clinical instability and readmission at 30 days were adjusted for PSI in only Adamuz and Halm studies.

Figure 2. Association between clinical instability at discharge and hospital readmissions (p=0.045)

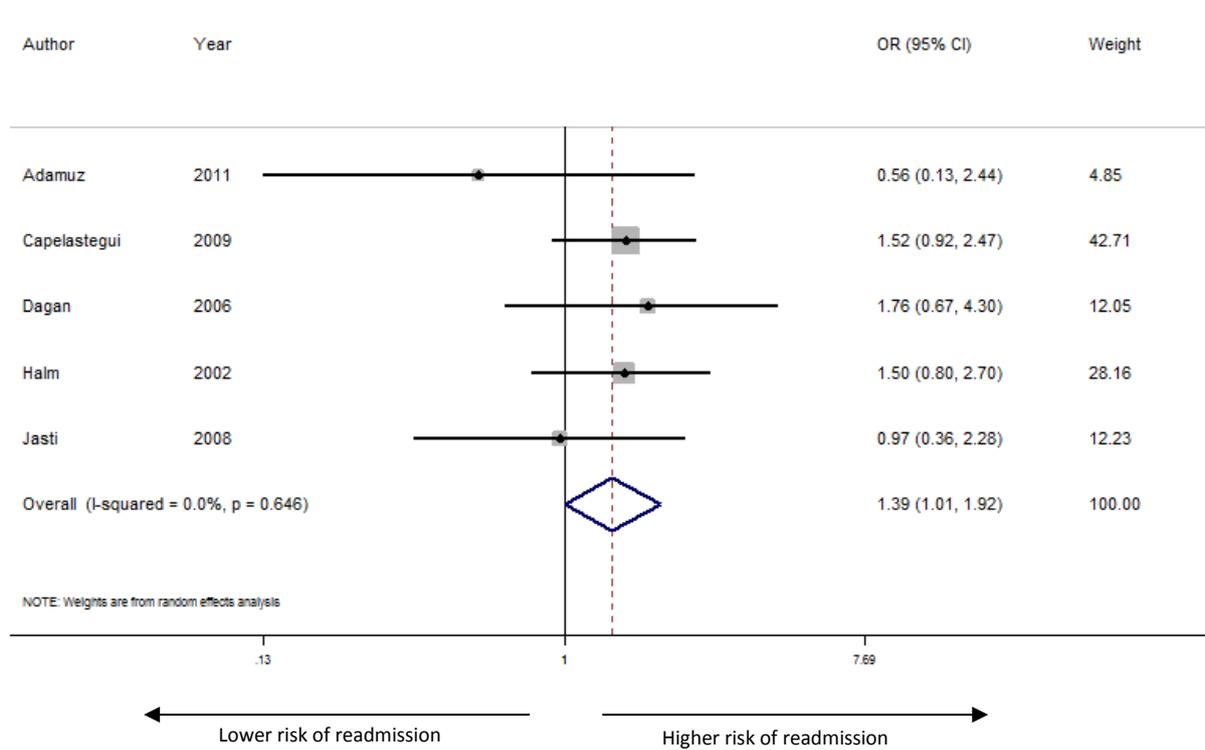


Figure 3. Funnel plot with pseudo 95% confidence limits

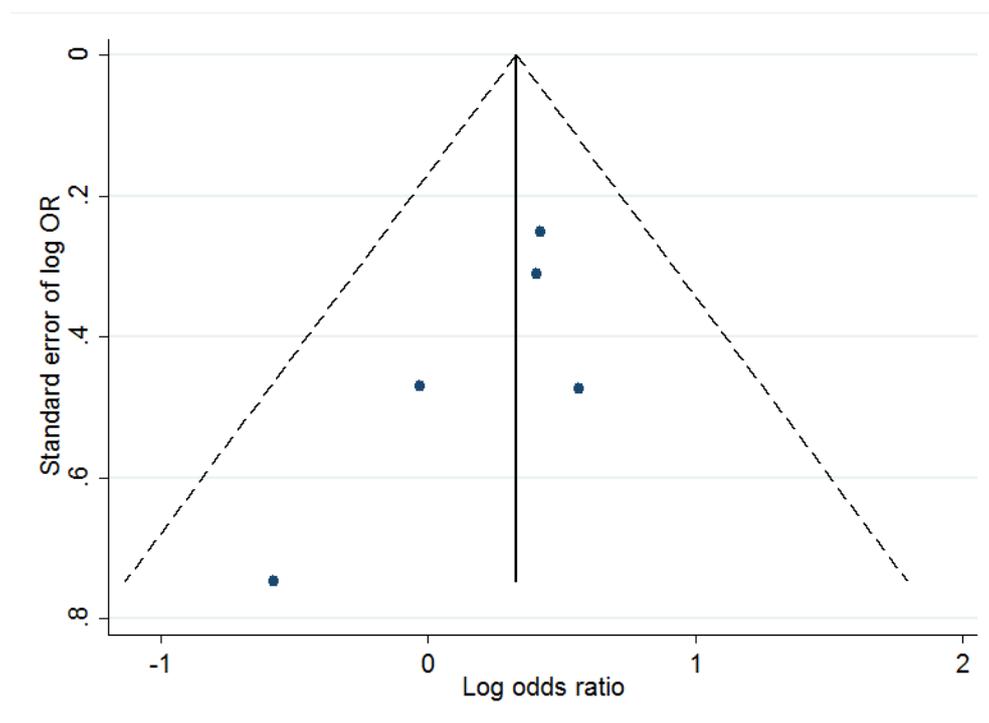


Table 3. Results of leave one-out sensitivity analysis

Study excluded	Pooled OR	(95% CI)	Heterogeneity I ² (%)
Adamuz, 2011	1.46	(1.05-2.03)	0.0
Capelastegui, 2009	1.30	(0.85-1.99)	0.0
Dagan, 2006	1.35	(0.95-1.90)	0.0
Halm, 2002	1.35	(0.92-1.97)	0.0
Jasti, 2008	1.46	(1.04-2.06)	0.0

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APPENDICES

Appendix 1. Search strategy used and results for Medline® the February 15, 2016

1	"Pneumonia"[Mesh]	79 538
2	pneumonia[TW]	122 941
3	CAP [TW]	32 792
4	((("Pneumonia"[Mesh]) OR pneumonia [TW]) OR CAP[TW])	156 365
5	"Patient Readmission"[Mesh]	10 040
6	readmi*[TW]	22 318
7	re-admi*[TW]	2 407
8	re-hosp*[TW]	906
9	rehosp*[TW]	4 202
10	(((((rehosp*[TW]) OR re-hosp*[TW]) OR re-admi*[TW]) OR readmi*[TW]) OR "Patient Readmission"[Mesh])	27 407
11	4 AND 10	806

Appendix 2. Primary study eligibility form on complete article

REF ID		Reviewer		Date	
Author, year					
Journal / Source					
Citation					
Publication type		<input type="checkbox"/> Full text <input type="checkbox"/> Abstract <input type="checkbox"/> Other , specify:			
Is the study a potential duplicate publication? (ex : PORT study, CAPO study, Medicaid, Medicare...)		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear Specify why:			
Other relevant publications as duplicate for clinical instability as risk factor (RF)		<input type="checkbox"/> No <input type="checkbox"/> Yes (please list in below) <input type="checkbox"/> NA			
Fate for clinical instability as RF		<input type="checkbox"/> Included without contacting authors <input type="checkbox"/> Decision pending, need for authors precisions <input type="checkbox"/> Use for discussion <input type="checkbox"/> Excluded with listing			

Other relevant citations as duplicate for clinical instability as RF

REF ID	Citation

Screening : other referencies as possibly relevant

None :

Author, year	REF ID (if already captured)	Citation

Eligibility assessment

Language			
<input type="checkbox"/> English	<input type="checkbox"/> French	<input type="checkbox"/> Spanish	<input type="checkbox"/> Russian <input type="checkbox"/> Other
Type of study			
Is the study described a original research? (with ≥30 participants)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Participants : inclusion criteria			
Were the participants adult?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Were the participants hospitalized for pneumonia?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Event of interest: readmission			
Does the study report data on readmission after discharge?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Characteristics of interest :			
Were the following characteristics assessed for hospitalized CAP patients?			<input type="checkbox"/> NA
Comorbidities	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Clinical prediction rules on admission	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Length of stay	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Strategy for antibiotic treatment	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Interventions	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Clinical instability on discharge	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Time to clinical stability	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Biological results on discharge	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Radiological results on discharge	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
Other(s)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
	Specify if yes :		
Comments			

Appendix 3. Data extraction form

REF ID	Reviewer	AMD	Date
Author, year			
Journal / Source			
Study ID registration			<input type="checkbox"/> Not reported
Citation			
Publication type	<input type="checkbox"/> Full text <input type="checkbox"/> Abstract <input type="checkbox"/> Other, specify:		
Other relevant publications	<input type="checkbox"/> No <input type="checkbox"/> Yes (see primary study eligibility form)		
Corresponding author details			
Principal investigator details			
Need to contact the author for precisions	<input type="checkbox"/> yes <input type="checkbox"/> no		Specify why :

Primary study characteristics

Study design	<input type="checkbox"/> Prospective cohort study <input type="checkbox"/> Retrospective or historical cohort study <input type="checkbox"/> Case control study <input type="checkbox"/> Nested case control study	<input type="checkbox"/> Individual randomized control trial <input type="checkbox"/> Cluster randomized control trial <input type="checkbox"/> Other Specify :
No. study centers	<input type="checkbox"/> Not reported	
Country/region	<input type="checkbox"/> USA <input type="checkbox"/> Canada <input type="checkbox"/> France <input type="checkbox"/> Spain <input type="checkbox"/> United Kingdom <input type="checkbox"/> Switzerland <input type="checkbox"/> Other, specify : <input type="checkbox"/> Not reported	
Date	Date study opened to accrual	<input type="checkbox"/> Not reported
	Date study closed to accrual	<input type="checkbox"/> Not reported
Comments		

Study Sample

Pneumonia type	exclusion of patients : <input type="checkbox"/> hospitalized in an acute care hospital for two or more days within 90 days of the infection <input type="checkbox"/> resided in a nursing home or long care facility <input type="checkbox"/> received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection <input type="checkbox"/> attended a hospital or hemodialysis clinic <input type="checkbox"/> none	
Pneumonia diagnostic criteria	<input type="checkbox"/> Clinical presentation <input type="checkbox"/> Clinical sings <input type="checkbox"/> X ray On admission or in the first 48 hours : <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unclear <input type="checkbox"/> ICD code <input type="checkbox"/> Other	
Specify pneumonia diagnostic criteria		
Exclusions criteria		<input type="checkbox"/> not reported
Number of subjects		<input type="checkbox"/> discharged alive
Lost to follow-up		
Not in the results		Reason : <input type="checkbox"/> death in hospital <input type="checkbox"/> Short stay <input type="checkbox"/> Other Specify :
Gender, <i>n/N (%)</i>	Male:	
	Female:	
	Not reported:	<input type="checkbox"/>

Age at enrollment, <i>year</i>	<input type="checkbox"/> not reported	<input type="checkbox"/> for all patients	<input type="checkbox"/> for patients discharged alive
	≥ 65 years, n/N (%)		
	Mean:		
	Standard deviation:		
	Median:		
	25 th percentile:		
	75 th percentile:		
	Lowest value:		
	Highest value:		

Outcome results

Length of follow-up (days)	Fixed at :	<input type="checkbox"/> 30 days <input type="checkbox"/> other Specify :		
	Since	<input type="checkbox"/> admission	<input type="checkbox"/> discharge	<input type="checkbox"/> unsure
	Mean:			
	Standard deviation:			
	Median:			
	25 th percentile:			
	75 th percentile:			
	Lowest value:			
	Highest value:			
	Not reported:	<input type="checkbox"/>		
In hospital death	n/N:			
	Rate, (%)			
Death after index hospital stay (H0)	at :	<input type="checkbox"/> 30 days <input type="checkbox"/> other Specify :		
	Since	<input type="checkbox"/> admission	<input type="checkbox"/> discharge	<input type="checkbox"/> unsure
	n/N:			
	Rate, (%)			
Deaths or readmission after H0	at :	<input type="checkbox"/> 30 days <input type="checkbox"/> other Specify :		
	Since	<input type="checkbox"/> admission	<input type="checkbox"/> discharge	<input type="checkbox"/> unsure
	n/N:			
	Rate, (%)			

Length of stay (days)	Sample	<input type="checkbox"/> for all patients	<input type="checkbox"/> for patients discharged alive
	Mean:		
	Standard deviation:		
	Median:		
	25 th percentile:		
	75 th percentile:		
	Lowest value:		
	Highest value:		
	Not reported:	<input type="checkbox"/>	

All causes readmission		<input type="checkbox"/> not assessed		
Comments				
Time to readmission (days)	Mean:			
	Standard deviation:			
	Median:			
	25 th percentile:			
	75 th percentile:			
	Lowest value:			
	Highest value:			
	Not reported:	<input type="checkbox"/>		
Readmission at 30 days*	Since	<input type="checkbox"/> admission	<input type="checkbox"/> discharge	<input type="checkbox"/> unsure
	n/N:			
	Rate, (%)			

* copy as many lines as needed for others timing of assessment

Specific readmissions (specific diag, unplanned..)†				<input type="checkbox"/> not assessed
Specific readmissions definition				
Time to readmission (days)	Mean:			
	Standard deviation:			
	Median:			
	25 th percentile:			
	75 th percentile:			
	Lowest value:			
	Highest value:			
	Not reported:	<input type="checkbox"/>		
Specific Readmission at 30d*	Since	<input type="checkbox"/> admission	<input type="checkbox"/> discharge	<input type="checkbox"/> unsure
	n/N:			
	Rate, (%)			

†copy the table as many as needed for each specific readmission used

* copy as many lines as needed for others timing of assessment

Data extraction

Confounders (conf) and risk factor (RF)

Characteristics‡	Conf or RF multi variable model, readmission at 30d as outcome*		matching	
	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
Age	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
Sex	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
Pneumonia severity or CURB 65	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
Comorbid conditions	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
....	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
....	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
....	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No
....	<input type="checkbox"/> yes	<input type="checkbox"/> No	<input type="checkbox"/> yes	<input type="checkbox"/> No

‡ copy as many line as needed

*copy as many table as needed for others outcomes

Description of risk factor in the all sample

RF	n/N (%) or mean \pm SD*

*otherwise precise if median (IQR)

Effects for clinical instability at discharge

All readmission risk (*copy the table for other outcome - eg : "avoidable readmission" or "pneumonia related readmission" or other timing after hospital stay - or for specific type of pneumonia - health care associated - or for specific aggregation - ≥ 2 criteria, specific score...*)

For each table specify the effect estimate (OR=, RR= or HR=) and the accuracy estimate (CI= or SE=)

≥ 1 clinical instability criteria	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95%CI)	ORa (95%CI)
no				
yes				

N+ : sample with readmitted with no missing data for the exposure : " ≥ 1 clinical instability criteria"

N- : sample with not readmitted with no missing data for the exposure: " ≥ 1 clinical instability criteria"

Blood pressure <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Heart rate <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Respiratory rate <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Temperature <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Oxygenation <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Mental status <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Ability to eat <i>specify unstable definition</i>	readmitted at 30 d n/N+	not readmitted at 30 d n/N-	Crude OR (95% CI)	ORa (95% CI)
no				
yes				

Appendix 4. Risk of bias and applicability grid

1- Study participation		
<i>Issues to consider</i>	<i>Rating</i>	<i>Text excerpts / comments</i>
The study sample and source population have similar distribution of :	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Age	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
Pneumonia severity	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
Comorbidities	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
The sampling frame and recruitment are adequate (e.g. : consecutive patients recruited)	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
There is adequate participation in the study by eligible individuals	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Period of recruitment is adequately described and covers all seasons	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Place of recruitment (setting and geographic location) are adequately described	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Inclusion and exclusion criteria are adequately described (e.g. explicit diagnostic criteria of CAP, adult population, exclusion of HP if patients not prospectively recruited)	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
<u>Risk of bias</u> (Likelihood that relationship between clinical stability and readmission is different for participants and eligible non-participants)	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	
<u>Concerns that the included patients do not match the review question?</u>	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	

2- Study attrition		
<i>Issues to consider</i>	<i>Rating</i>	<i>Text excerpts / comments</i>
Response rate (i.e., proportion of study sample completing the study and providing readmission data) is adequate	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Reasons for loss to follow-up not linked to clinical stability status or readmission (e.g. at random)	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure <input type="checkbox"/> Non applicable	
There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not, for :	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure <input type="checkbox"/> Non applicable	
Age	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
Pneumonia severity	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
Comorbidities	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
Readmissions	<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unsure	
<u>Risk of bias</u> (Likelihood that relationship between clinical instability and readmission are different for completing and non-completing participants <i>or in others words that loss to follow-up is associated with key characteristics</i>)	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	

3- Clinical instability measurement		
<i>Issues to consider</i>	<i>Rating</i>	<i>Text excerpts / comments</i>
A clear definition or description of clinical instability is provided (e.g. criteria definition, threshold, timing...)	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Method of clinical instability measurement is adequately valid and reliable to limit misclassification bias	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure <input type="checkbox"/> non applicable	
The method and setting of measurement of clinical instability is the same for all study participants	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Adequate proportion of the study sample has complete data for clinical instability variable	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Appropriate methods of imputation are used for missing 'clinical instability ' data	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure <input type="checkbox"/> non applicable	
<u>Risk bias</u> (Differential measurement of clinical instability related to the level of readmission)	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	

4- Readmission measurement		
<i>Issues to consider</i>	<i>Rating</i>	<i>Text excerpts / comments</i>
A clear definition of hospital readmission is provided (all versus specific) along with timing (period in days after index hospitalization and beginning of measurement : admission versus discharge of index hospitalization)	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
The method of hospital readmission measurement used is adequately valid and reliable to limit misclassification bias : all readmissions caught (<i>e.g.</i> in all possible hospitals and during the all pre-specified follow-up)	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
The method and setting of readmission measurement is the same for all study participants	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
<u>Risk of bias</u> (Differential measurement of readmission related to the baseline level of clinical instability).	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	
<u>Concerns that the included readmission not match the review question?</u>	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	

5- Study confounding		
<i>Issues to consider</i>	<i>Rating</i>	<i>Text excerpts / comments</i>
All-important confounders (age, pneumonia severity, comorbid conditions) are measured.	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Age	<input type="checkbox"/> yes <input type="checkbox"/> no	
Pneumonia severity or CURB 65	<input type="checkbox"/> yes <input type="checkbox"/> no	
Comorbidities	<input type="checkbox"/> yes <input type="checkbox"/> no	
Clear definitions of the important confounders measured are provided	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Pneumonia severity or CURB 65	<input type="checkbox"/> yes <input type="checkbox"/> no	
Comorbidities	<input type="checkbox"/> yes <input type="checkbox"/> no	
Measurement of all important confounders (PS and comorbidities) is adequately valid and reliable.	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
The method and setting of confounding measurement are the same for all study participants	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Appropriate methods of imputation are used for missing confounder data	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure <input type="checkbox"/> non applicable	
Important potential confounders (age, PS, comorbidities) are accounted for in the study design or by adjustment	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Age	<input type="checkbox"/> yes <input type="checkbox"/> no	
Pneumonia severity or CURB 65	<input type="checkbox"/> yes <input type="checkbox"/> no	
Comorbidities	<input type="checkbox"/> yes <input type="checkbox"/> no	
<u>Risk of bias</u>	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	

6- Statistical Analysis and Reporting		
<i>Issues to consider</i>	<i>Rating</i>	<i>Text excerpts / comments</i>
There is sufficient presentation of data to assess the adequacy of the analysis	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
The selected statistical model is adequate for the design of the study	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
Selective reporting of results avoided	<input type="checkbox"/> yes <input type="checkbox"/> partial <input type="checkbox"/> no <input type="checkbox"/> unsure	
<u>Risk of bias</u>	<input type="checkbox"/> high <input type="checkbox"/> low <input type="checkbox"/> unclear	

Appendix 5. List of potentially eligible records excluded with no full text assessment

- Language other than English, French, Russian or Spanish:

Aoshima MS, T. ; Uchiyama, N. ; Chonabayashi, N. [Usefulness of clinical pathway for community-acquired pneumonia as both an educational and a cost-management tool--an intervention study to compare the usefulness of management with a critical pathway to historical control of conventional management]. *Nihon Kokyuki Gakkai Zasshi* 2002; 40:644-652

Eagan TG, A. ; Morkve, O. ; Skaug, K. [Hospital admissions due to obstructive lung diseases and pneumonia in two hospital districts]. *Tidsskr Nor Laegeforen* 1999; 119:4173-4175

Uchiyama NA, M. ; Satoh, T. ; Chonabayashi, N. [The efficacy of switch therapy in community-acquired pneumonia in Japan]. *Nihon Kokyuki Gakkai Zasshi* 2003; 41:261-267

- Full text article not retrieved:

Study prompts overhaul of COPD/pneumonia care. *Hosp Peer Rev* 1996; 21:121-122; suppl 122 p

Cut pneumonia length of stay, costs, readmissions. *Health Care Cost Reengineering Rep* 1998; 3:1-5; suppl 1-4

Baser OL, X. ; Phatak, H. ; Wang, L. ; Mardekian, J. ; Kawabata, H. ; Petersel, D. ; Hamilton, M. ; Ramacciotti, E. Venous thromboembolism prophylaxis and clinical consequences in medically ill patients. *Am J Ther* 2013; 20:132-142

Bohannon RWM, R. D. Hospital readmissions of elderly patients hospitalized with pneumonia. *Conn Med* 2003; 67:599-603

Englert JD, K. M. ; Koch, K. E. Using clinical practice analysis to improve care. *Jt Comm J Qual Improv* 2001; 27:291-301

Flanagan JS, K. D. ; Gregas, M. ; Shindul-Rothschild, J. Predictors of 30-Day Readmission for Pneumonia. *J Nurs Adm* 2016; 46:69-74

Halley HJ. Approaches to drug therapy, formulary, and pathway management in a large community hospital. *Am J Health Syst Pharm* 2000; 57 Suppl 3:S17-21

Hand RP, F. ; Klemka-Walden, L. ; Incauskis, D. Use of statistical control charts to assess outcomes of medical care: pneumonia in Medicare patients. *Am J Med Sci* 1994; 307:329-334

Hedlund J. Community-acquired pneumonia requiring hospitalisation. Factors of importance for the short-and long term prognosis. *Scand J Infect Dis Suppl* 1995; 97:1-60

Hedlund JH, L. O. ; Ortvist, A. Short- and long-term prognosis for middle-aged and elderly patients hospitalized with community-acquired pneumonia: impact of nutritional and inflammatory factors. *Scand J Infect Dis* 1995; 27:32-37

Hemenway ANN, M. A. Impact of Antibiotic Choice on Pneumonia Readmission Rates. *Am J Ther* 2015

Hendrickson JRN, D. S. Pharmacoeconomic benefit of antibiotic step-down therapy: converting patients from intravenous ceftriaxone to oral cefpodoxime proxetil. *Ann Pharmacother* 1995; 29:561-565

Hilbert JPZ, S. ; Keyser, D. J. ; Peele, P. B. Using decision trees to manage hospital readmission risk for acute myocardial infarction, heart failure, and pneumonia. *Appl Health Econ Health Policy* 2014; 12:573-585

Johnson CCM, M. ; Epstein, S. M. ; Lee, J. D. The effect of a physician education program on hospital length of stay and total patient charges. *J S C Med Assoc* 1993; 89:293-301

Levenson D. Simple measure predicts how pneumonia patients will fare after discharge. *Rep Med Guidel Outcomes Res* 2002; 13:7-9

Radhakrishnan KJ, T. L. ; Weems, D. ; Knight, T. W. ; Rice, W. H. Seamless Transitions: Achieving Patient Safety Through Communication and Collaboration. *J Patient Saf* 2015

- Sherer YB, E. ; Rotman, P. ; Levy, Y. ; Shoenfeld, Y. Comparative clinical study of cefonicid, chloramphenicol, and penicillin in community-acquired pneumonia. *Int J Mol Med* 1998; 2:343-348
- Torres OHG, E. ; Comas, M. T. ; Saez, M. E. ; Clotet, S. ; Ramirez, H. D. ; Mateo, M. ; Ruiz, D. [Impact of a multidimensional intervention in elderly patients with community-acquired pneumonia: IMIEPCAP clinical trial]. *Rev Esp Geriatr Gerontol* 2016; 51:37-43
- Weitzman SH, D. ; Naggan, L. ; Bar-Ziv, G. ; Glick, S. Uncomplicated pneumonia: an evaluation of determinants of length of hospitalization. *Isr J Med Sci* 1983; 19:591-595

Appendix 6. Diagnostic of pneumonia in included studies.

Reference	Diagnostic criteria	Exclusion of HCAP* (yes/no)
Adamuz, 2011	-	no
Capelastegui, 2009	CAP was defined as pulmonary infiltrates seen on chest radiograph not known to be old and symptoms that were consistent with pneumonia	Partial : nursing home resident
Dagan, 2006	Based on final diagnostic on discharge letter "CAP"	no
Halm, 2002	One or more symptoms suggestive of pneumonia and radiographic evidence of pneumonia within 24 hours of presentation	no
Jasti, 2008	"Clinical diagnosis of and documented treatment plan for pneumonia and the presence of an acute pulmonary infiltrate on chest radiography at presentation"	no

* HCAP : Health Care Associated Pneumonia include patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection ; resided in a nursing home or long care facility ; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection ; attended a hospital or hemodialysis clinic²⁴.

Appendix 7. Clinical instability criteria definition and prevalence among discharged patients

	Timing	SBP	N (%)	HR	N (%)	RR	N (%)	T°C	N (%)	Oxygenation	N (%)	mental status	N (%)	inability to eat	N (%)
Adamuz, 2011 [¥]	all measurements in the 24-hour before discharge	< 90	-	>100	-	>24	28 (3.6) [§]	>37.8	-	sat < 90%*	26 (3.3) [§]	abnormal or not backed to baseline	-	yes/no	-
Capelastegui, 2009	on hospital discharge	≤ 90	-	≥120	-	≥24	-	≥ 37.2	-	sat < 90%**	-	-	-	no†	-
Dagan, 2006	last day of hospitalization	≤ 90	7 (1.9)	>100	42 (11.3)	>24	6 (1.6)	rectal >37.8	4 (1.1)	sat < 90%	21 (5.6)	change of mental status compared to the baseline	13 (3.5)	yes/no	14 (3.8)
Halm, 2002	in the 24 hour prior to discharge	< 90	7 (1.0)	>100	24 (3.5)	>24	26 (3.8)	oral >37.8	23 (3.4)	sat < 90%*	40 (5.9)	abnormal or not backed to baseline	11 (1.6)	yes/no	13 (1.9)
Jasti, 2008	within 24h before discharge	< 90	6 (1.0)	>100	13 (2.3)	>24	14 (2.4)	>37.8	4 (0.7)	sat < 90%	25 (4.3)	-	-	-	-

SBP : Systolic Blood Pressure ; HR : Heart Rate ; RR : Respiratory Rate

[¥]assessment of clinical instability made as : Halm EA, Fine MJ, Marrie TJ et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998; 279: 1452–7 and clinical stability criteria as defined by Halm, 2002⁹

[§] Percentages exclude patients with missing data

* or PaO₂<60mmHg or sat <95% if O₂ by nasal prongs or mechanical ventilation or O₂ by face mask

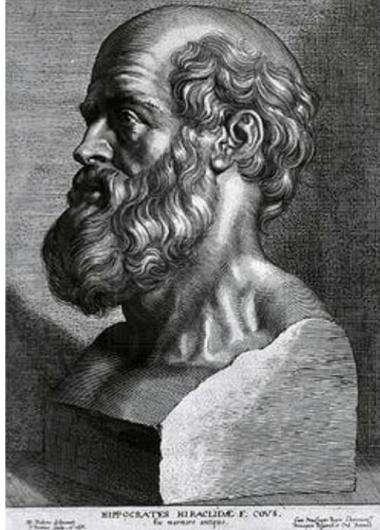
** or PaO₂<60mmHg or mechanical ventilation or oxygen by face mask or nasal prongs

†all patients at discharge were able to eat and receive oral medication

Appendix 8. Details on assumptions made to compute crude OR for Capelastegui study²²

Item	No.
Patients discharged alive included in the analytical sample	1,117
All-cause hospital readmissions within 30 days of discharge	81
Instability factors on hospital discharge reported (399+684) (Table 1) [§]	1083
≥ 1 instability factors on hospital discharge (Table 1) [§]	399
Pneumonia-related readmissions within 30 days of discharge (Tables 2-4) [§]	29
Pneumonia-related readmissions within 30 days of discharge (Tables 5) [§]	27
Pneumonia-unrelated readmissions within 30 days of discharge (Tables 2-4) [§]	52
Pneumonia-unrelated readmissions within 30 days of discharge (Tables 5) [§]	51
≥ 1 instability factors on hospital discharge for pneumonia-related readmissions (Table 5 [§] + footnote : 351 +48)	399
0 instability factor on hospital discharge for pneumonia-related readmissions (Table 5 [§] + footnote : 620 + 64)	684
Pneumonia-related readmissions for patients with ≥ 1 instability factors on hospital discharge (Table 5 [§] + footnote : 11+6)	17
Pneumonia-related readmissions for patients with 0 instability factor on hospital discharge (Table 5 [§] + footnote : 9 + 1)	10
Pneumonia-unrelated readmissions for patients with ≥ 1 instability factors on hospital discharge (399*51/1083) under the null hypothesis that clinical instability is not associated with pneumonia-unrelated readmission) TBV with the authors	19
Pneumonia-unrelated readmissions for patients with 0 instability factor on hospital discharge (684*51/ 1083) under the null hypothesis that clinical instability is not associated with pneumonia-unrelated readmission) TBV with the authors	32

[§]Tables cited are in Capelastegui, 2009 report²²



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Clinical instability on discharge and hospital readmissions in adult patients hospitalized with community-acquired pneumonia: a systematic review with meta-analysis

RESUME

Objectifs : Evaluer l'association entre l'instabilité clinique à la sortie et la réadmission chez des patients adultes hospitalisés pour pneumonie aiguë communautaire.

Méthode : Nous avons réalisé une revue systématique avec méta-analyse de données agrégées. Les études originales ont été identifiées via les bases bibliographiques Medline® et Central® depuis leur date de création jusqu'au 15 février 2016. Les études éligibles incluaient au moins 30 patients adultes hospitalisés pour pneumonie. L'odds ratio commun a été estimé par modèle à effets aléatoires.

Résultats : Parmi les 874 références identifiées par notre stratégie de recherche, cinq études ont été incluses dans la méta-analyse totalisant 3575 individus. L'association entre instabilité clinique et réadmission était statistiquement significative (OR=1,39, intervalle de confiance à 95% de 1,01 à 1,92, P=0,045). Aucune hétérogénéité entre études n'a été constatée ($I^2=0,0\%$) malgré des définitions de l'instabilité clinique légèrement différentes. Ce résultat était robuste en analyse de sensibilité réalisée par « leave-one-out ». Les données à disposition ne permettaient pas de considérer séparément les réadmissions évitables.

Conclusion : Présenter au moins un critère d'instabilité clinique au moment de la sortie est associé à un risque accru de réadmission chez les patients adultes hospitalisés pour pneumonie aiguë communautaire. Cependant, comme dans toute méta-analyse de données issues d'études observationnelles, un potentiel biais de confusion ne peut être écarté. Une méta-analyse de données individuelles permettrait de discuter de la pertinence des critères et de leurs seuils à utiliser.

MOTS CLEFS : pneumonie aiguë communautaire, instabilité clinique, réadmission

ABSTRACT

Aims : To assess the association between clinical instability at discharge and readmission for hospitalized adult patients with community-acquired pneumonia.

Method : We performed a systematic review with meta-analysis of aggregated data. Primary studies were identified by searching Medline® and Central® databases from inception to February 15, 2016 and by screening references of potential eligible records. Eligible studies of all designs included at least 30 adult patients hospitalized for pneumonia. Pooled odds ratio was estimated by random effect model.

Results : Of the 874 records retrieved from our search process, five studies were included in the meta-analysis totaling 3575 participants. Association between clinical instability and readmission was statistically significant (OR=1.39, 95% confidence interval 1.01 to 1.92, P=0.045). No evidence of between studies heterogeneity ($I^2=0.0\%$) was found despite different clinical instability definitions. This result was robust in sensitivity analysis by leave-one-out method. Data at disposal did not allow us to consider avoidable readmission apart.

Conclusions: Presenting at least one criterion of clinical instability at discharge is associated with higher risk of readmission in adult patients hospitalized for community acquired pneumonia. However, as in any meta-analysis of data from observational studies, confounding effects cannot be discarded. A meta-analysis of individual participant data could allow the discussion of clinical stability best definition by considering each criterion relevance and threshold.

KEYWORDS: community-acquired infections, pneumonia, clinical instability, readmission