Misdiagnosis of community-acquired pneumonia in patients admitted to respiratory wards, Penang General Hospital

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ABSTRACT

Introduction: Pneumonia continues to be as one of the top causes of hospitalisations and deaths in Malaysia despite the advancement in prevention and treatment of pneumonia. One of the possible explanations is the frequent misdiagnosis of pneumonia which had been reported elsewhere but such data is not available locally.

Objectives: This is an audit project aiming to evaluate the proportion of misdiagnosis among hospitalised community-acquired pneumonia (CAP) patients in the Respiratory wards of Penang General Hospital based on their initial presentation data, and their associated outcomes.

Methods: We reviewed the medical notes and initial chest radiographs of 188 CAP patients who were admitted to respiratory wards. Misdiagnosis was defined as cases which lack suggestive clinical features and/or chest radiograph changes. In-hospital mortality and length of stay (LOS) were the outcomes of interest.

Results: The study found that 38.8% (n=73) of the hospitalised CAP patients were misdiagnosed. The most common alternative diagnosis was upper respiratory tract infection (32.8%, n=24). There was no statistical difference between misdiagnosis and CAP patients in the demographic and clinical variables collected. In terms of outcomes, misdiagnosed patients were discharged earlier (mean LOS= 3.5±3.28 days vs. 7.7±15.29 days, p=0.03) but the in-hospital mortality difference was not statistically significant (p=0.07).

Conclusions: One third of our CAP admissions were misdiagnosed. Although initial misdiagnosis of CAP in our study did not show any increase in mortality or morbidity, a proper diagnosis of CAP will be helpful in preventing inappropriate prescription of antibiotics and unnecessary admission.

KEY WORDS:
Diagnostic Errors, Pneumonia, Practice, Retrospective Studies

INTRODUCTION

Pneumonia is a major health problem causing significant morbidity and mortality worldwide.[1-3] The Statistics Department of Malaysia reported that for the past 10 years, pneumonia remains one of the biggest causes of death.[4] In terms of health care cost, pneumonia accounted for 4205 cases per every 100,000 admissions in public hospitals in Malaysia and the average cost per admission due to pneumonia was an enormous? USD1177.50.[5] However, most of the data pertaining pneumonia in this country was derived from administrative data which may be unreliable especially with its early clinical diagnostic uncertainty.[2,3]

Pneumonia is usually categorised based on the site of acquisition and the most common type of pneumonia diagnosed is community-acquired pneumonia (CAP).[3] However, the diagnosis of pneumonia is both challenging and uncertain. The gold standard for diagnosis is detection of the microorganisms in the lung tissues[6] but this is neither practical nor safe as it takes more than 48 hours to obtain the definitive diagnosis. Delay in diagnosis leads to delay in initiation of treatment which could be harmful to patients.[7,8] Hence in practice, diagnosis is made clinically and thus misdiagnosis is very common.

Prevalence of misdiagnosis of CAP had been previously reported to be from 17% to 44.7% elsewhere.[9-14] This is mostly due to the low specificity of the diagnostic components of pneumonia, namely the presence of associated clinical features and the presence of parenchymal infiltrates on imaging (most commonly by chest radiography). The clinical features vary widely and may encompass the differential diagnosis of most respiratory conditions. Hence it is difficult to diagnose CAP based on clinical features.[15-18] Similarly, the chest radiograph's interpretation is often uncertain with poor concordance between readers and the appearance of infiltrates can be delayed or distorted by co-existing co-morbidities.[19-24] Despite our great medical advancement in recent years, the diagnostic accuracy of pneumonia itself remains a hurdle to be overcome.

Despite all of the above, there is no data on the frequency of misdiagnosis in Malaysia. In fact, pneumonia is greatly

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neglected in research locally and as mentioned, only administrative data are available to provide any indication of its clinical situation. Thus, we conducted an audit to retrospectively evaluate the accuracy of admission diagnosis of CAP patients who were admitted to the Chest wards of Penang General Hospital and their associated outcomes. The evaluation is based on initial chest radiographs and clinical profiles.

METHODS

This audit study was conducted in the Chest wards with a total of 60 bed capacity. All patients above age of 18 who were admitted from the accident and emergency department (A&E) to chest wards with a primary or secondary diagnosis of CAP between 1st June 2018 and 31st November 2018 were included. Patients who were transferred from other wards or hospitals were excluded. Other exclusion criteria were cases with more than 20% of missing data, foreigners, pregnant women or patients involved in medico-legal cases. Foreigners are excluded as often they have inadequate clinical features documentations due to language barriers and have very different care seeking behaviour. Pregnant women are excluded as they had significantly lower admission threshold, high refusal of chest radiographs (as local practice requirement of thorough consent taking) and lack of consistency in admission decision to our wards. Lastly, the medico-legal cases are not included due to complexity involved in retrieving medical notes.

Clinical notes and laboratory results system were accessed to collect the data of demographics (age, gender, ethnicity), smoking history, underlying chronic co-morbidities, symptoms of pneumonia (fever, rigours, cough, chest pain, sputum change, dyspnoea and sweats), vital signs (BP, pulse and respiratory rate, temperature) and blood parameters sent routinely (blood counts, biochemistry and arterial blood gases) upon presentation to A&E. In addition, occurrence of temperature spikes in the ward, requirement for ventilator and inotropic support in the ward, transfer to Intensive Care Unit (ICU), length of stay (LOS) in hospital and mortality during hospitalisation were recorded. Admission chest radiographs were also obtained for evaluation.

In accordance to international guidelines[1,25], the study defined misdiagnosis of CAP as cases which lack suggestive clinical features and chest radiograph changes. In the event of only one component being present, the decision would be based on the discretion of the reviewers who consisted of experienced and qualified specialists in respiratory and internal medicine. However, only the initial clinical features and initial chest radiographs at presentations were reviewed to evaluate the CAP diagnosis appropriateness made on admission.

The prevalence of initial misdiagnosis of CAP was calculated by dividing the number of misdiagnosed cases with the total number of subjects. The comparison of clinical factors between the misdiagnosis and CAP was performed using Students T-test and Pearson's χ^2 test as appropriate. Data analysis was performed using SPSS software, version 21.0; SPSS Inc; Chicago, IL, USA.

The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Medical Research Ethics Committee (NMRR-18-1997-42641-IIR). Sample size was calculated using the Power and Sample Size Calculator.[26] Previous studies showed that the rate of CAP misdiagnosis ranged from 17% to 44.7%. The population size of CAP admissions is estimated to be 350. Calculated with 80% certainty (power) and alpha of 0.05, the number required in this retrospective study is at least 183 patients.

RESULTS

The study analysed a total of 234 patients who were admitted to the respiratory wards with primary or secondary diagnosis of CAP and in all 46 cases were excluded. Majority of the exclusions were due to incomplete data (n=31), transfer from other hospitals or wards (n=13) and pregnant patients (n=2).

Of the 188 patients included, most of them were males (n=114, 60.6%), Chinese (n=96, 51.1%) and non-smokers (n=79, 42%). The mean age was 65.5 (SD16.89) years and majority have underlying co-morbidities, most commonly obstructive lung diseases (n=61, 32.5%). The most common presenting complaints were cough (n=150, 79.8%), dyspnoea (n=136, 72.3%) and fever (n=116, 61.7%). In the A&E, 46.3% (n=87) had a documented fever (temperature >37.8°C) and 54.8% (n=103) had SpO2 of less than 93%. Baseline blood tests including blood counts and biochemistry were done on all patients and arterial blood gas performed on 95.2% (n=179) patients. While in the ward, 11.2% (n=21) required mechanical ventilation and inotropic support and 8.0% (n=15) needed transfer to ICU. The overall mortality rate was 12.8% (n=24) and mean LOS was 6.04 (SD12.18) days. (Table I)

All patients had an initial chest radiographs performed prior to admission. On evaluation by the investigators, only 75 (39.9%) chest radiographs were found to have changes suggestive of pneumonia, 52 (27.7%) were deemed equivocal and the remaining 61 (32.4%) did not have radiographic changes to suggest pneumonia (Table II).

Based on the evaluation of initial clinical features and the initial chest radiographs, 38.8% (n=73) of the admission diagnosis of CAP were considered as misdiagnosis. These cases had been reviewed carefully by the investigators for alternative diagnoses. Upper respiratory tract infection (32.8%, n=24) and heart failure (13.7%, n=10) were the most common alternative diagnoses. Notably, 15% (n=11) of the cases were assigned "unlikely CAP" but without alternative diagnosis (Table III).

There was no significant different between the misdiagnosed patients and the CAP patients in terms of demographics, clinical presentations and blood parameters. However, misdiagnosed patients were more likely to be discharged earlier, with shorter mean LOS at 3.5±3.28 days in comparison with the mean LOS of the CAP group at 7.7±15.29 days (p=0.03). Although the in-hospital mortality in CAP group were higher (16.5% vs. 6.8%), this difference was not statistically significant (p=0.07) (Table IV).

Table I: Baseline demographics, clinical characteristics and outcomes of 188 patients included in the study

Variables		
Age (in years), mean (SD)		65.5 (16.89)
Gender	Male, n(%)	114 (60.6)
	Female, n(%)	74 (39.4)
Ethnicity	Malay, n(%)	59 (31.4)
	Chinese, n(%)	96 (51.1)
	Indian, n(%)	33 (17.6)
Smoking Status	Current Smoker, n(%)	48 (25.5)
	Ex-smoker, n(%)	34 (18.1)
	Non-smoker, n(%)	79 (42.0)
Underlying co-morbidities	Obstructive Lung Disease, n(%)	61 (32.5)
	Chronic Heart Failure, n(%)	30 (16)
	Cancer (any type), n(%)	18 (9.6)
	Chronic Kidney Disease (eGFR* <60), n(%)	20 (10.6)
Symptoms of Pneumonia	Fever, n(%)	116 (61.7)
	Rigors, n(%)	20 (10.4)
	Sweat, n(%)	3 (1.6%)
	Cough, n(%)	150 (79.8)
	Sputum Change, n(%)	89 (47.3)
	Chest Discomfort, n(%)	34 (18.1)
	Dyspnoea, n(%)	136 (72.3)
Findings in Emergency Department	Fever (>37.8C), n(%)	87 (46.3)
	Pulse oximeter oxygen saturation (<93%), n(%)	103 (54.8)
	Leukocytosis (White Blood Cell >10 x 103/uL)	120 (63.8)
	Partial Pressure of Oxygen Arterial Blood (<60mmHg), n(%)	73 (40.8)
Progress in ward	Temperature during ward stay (>37.8C), n(%)	56 (29.8)
	Requiring Mechanical Ventilation, n(%)	21 (11.2)
	Requiring Inotropic Support, n(%)	21 (11.2)
	Transferred to Intensive Care Unit, n(%)	15 (8.0)
Total Length of Stay (in days), mean (SD)		6.04 (12.18)
In-hospital Mortality, n(%)		24 (12.8%)

* Estimated Glomerular Filtration Rate

Table II: Interpretation of the Initial Chest Radiograph by Investigators

	n, (%)
Changes suggestive of Pneumonia	75 (39.9%)
Equivocal	52 (27.7%)
Changes unlikely to suggest Pneumonia	61 (32.4%)

Table III: Alternative diagnosis assigned to misdiagnosed cases upon review by the investigators

Alternative diagnosis (N=73)	**n (%)**
Upper respiratory tract infection,	24 (32.8)
Heart failure	10 (13.7)
Non-infective exacerbation of chronic lung disease	6 (8.2)
Acute coronary syndrome	4 (5.5)
Non specific viral fever	4 (5.5)
Progression of lung cancer	4 (5.5)
Exacerbation of obstructive sleep apnoea	3 (4.1)
Cellulitis	3 (4.1)
Urinary tract infection	2 (2.7)
Dengue Fever	1 (1.4)
Scabies	1 (1.4)
Unlikely Community-acquired Pneumonia	11 (15)

Table IV: Comparison of demographics, clinical characteristics and outcomes between CAP and Misdiagnosis of CAP

		CAP	Misdiagnosis	P value
Demographics				
Age, in years, mean (SD)		65.28 (17.82)	65.87 (14.42)	0.816 *
Male gender, n(%)		69 (60%)	45 (61.6%)	0.879 ‡
Ethnicity	Malay, n(%)	33 (28.7%)	26 (35.6%)	0.441 ‡
	Chinese, n(%)	59 (51.3%)	37 (50.7%)	
	Indian, n(%)	23 (20%)	10 (13.7%)	
Clinical Characteristics at A&E				
Underlying chronic obstructive lung disease, n(%)		31 (27%)	30 (41.1%)	0.055 ‡
- Bronchial Asthma		13	14	
- COPD		18	16	
Underlying chronic heart failure, n(%)		15 (13%)	15 (20.5%)	0.220 ‡
Non-Smoker, n(%)		49 (42.6%)	30 (41.1%)	0.974 ‡
Presented with fever, n(%)		51 (44.3%)	28 (38.4%)	0.451 ‡
Presented with rigors, n(%)		12 (10.4%)	8 (11%)	>0.999 ‡
Presented with sweat, n(%)		2 (1.7%)	1 (1.4%)	>0.999 ‡
Presented with cough, n(%)		94 (81.7%)	56 (76.7%)	0.604 ‡
Presented with sputum change, n(%)		58 (50.4%)	31 (42.5%)	0.298 ‡
Presented with chest discomfort, n(%)		20 (17.4%)	14 (19.2%)	0.846 ‡
Presented with dyspnoea, n(%)		82 (71.3%)	54 (74%)	0.740 ‡
Mean Arterial Pressure, mmHg, mean(SD)		95.97 (21.03)	101.03 (16.01)	0.064*
Pulse rate per minute, mean (SD)		105.84 (20.36)	102.64 (26.82)	0.357*
Fever, temperature >37.8C, n(%)		54 (47%)	33 (45.2%)	0.881 ‡
Respiratory rate, per minute, mean(SD)		24.6 (5.54)	23.9 (5.68)	0.447*
Pulse Oximetry (SpO2 <93%), n(%)		61 (53%)	42 (57.5%)	0.552 ‡
Leukocytosis (Total White Cell > 10 x 103/uL), n(%)		72 (63.2%)	48 (67.6%)	0.805 ‡
Urea in mmol/L, mean (SD)		8.01 (4.81)	7.28 (8.70)	0.460*
Albumin in mmol/L, mean (SD)		28.78 (6.56)	30.38 (6.99)	0.212*
PaO2 < 60mmHg on ABG, n(%)		51 (46.4%)	22 (31.9%)	0.062 ‡
Outcomes				
Length of Stay, in days, mean(SD)		7.73 (15.29)	3.5 (3.28)	0.022 *
In-hospital Mortality, n(%)		19 (16.5%)	5 (6.8%)	0.072 ‡

* Students T**x**-test

‡ Pearson's ^{2} test

DISCUSSION

This maybe the very first clinical study in the South East Asian region looking into the accuracy of initial clinical diagnosis of CAP made in usual clinical practice. Our findings that 38.8% of CAP hospitalisations were misdiagnosed was not far from the findings previously reported, although different methodologies were applied.

Kanwar et al reported that 36% to 44.7% of the CAP diagnosis on admission to hospital did not fulfil the defined clinical diagnostic criteria of their study.[9] Their diagnostic criteria of CAP were the presence of chest radiography findings with at least one clinical features of pneumonia, which was quite similar to our study. Similarly, Brendish et al. reported that 28.2% of patients with a diagnosis of pneumonia had no radiological evidence of pneumonia. Conversely, 34.9% patients with clinico-radiological evidence of pneumonia did not have a diagnosis of pneumonia upon discharge.[10]

A possible argument maybe that the retrospective reviews of the diagnosis of such cases maybe biased and does not reflect the true scenario of the clinical practice. Addressing that, Chandra and colleagues retrospectively reviewed 800 patients who were admitted from the A&E as CAP and found that 27.3% ultimately went home with a non-pneumonia diagnosis.[11] The study provides an interesting set of data as this is not a retrospective revision of diagnosis like our study. As our study aimed at evaluating the initial diagnosis on admission, we did not capture the discharge diagnosis and hence we were unable to replicate the work of Chandra et al.

A major concern about to the uncertainty of the clinical diagnosis of CAP is the low specificity of the interpretation of the chest radiograph being used as the diagnostic criteria. Some authors investigated the value of using more advanced imaging methods to diagnose accurately CAP. For example, Claessen et al., reported that the addition of early CT scan led to a change of CAP diagnosis in 59% of patients enrolled in the study (probability of pneumonia was lowered in 40% of cases and raised in 19% of cases).[12] Similarly, Prenvik et al., utilised low dose CT scan in elderly CAP patients and reported that 45% of the diagnosis needed modifications.[13] Both studies pointed out that the current practice in diagnosing CAP is still very much an educated guesswork.

The similarity between the misdiagnosed and the retrospectively diagnosed CAP patients in terms of demographic and clinical profile in our study was one of the reasons why the accurate CAP diagnosis was challenging. This finding was in contrast to the BTS audit report which found that adults misdiagnosed as having CAP were older with more comorbidities, possessed fewer chest symptoms but more constitutional symptoms and had lower in-patient mortality.[14]

Interestingly, the co-morbidity of obstructive lung disease was almost statistically significant between CAP and

misdiagnosis of CAP (p=0.055, Table IV). Patients with underlying obstructive lung disease (bronchial asthma and chronic obstructive pulmonary disease) are often over-diagnosed with CAP upon presentation to hospitals as the chest radiographs were mostly abnormal and patients are more symptomatic and hence more likely to be treated with antibiotics as CAP.

It is also important to point out that tuberculosis is an interesting aspect of CAP which was omitted from this study. This study only looked at the accuracy of CAP diagnosis based on initial presentation data. Hence if the patients had obvious features of tuberculosis and diagnosed as such, they would not have been included in the study. The study was only to detect inaccuracies of CAP diagnosis, such as cases obviously tuberculosis but misdiagnosed as CAP. Fortunately, we did not find such cases. However, CAP cases without obvious features of tuberculosis but later diagnosed as tuberculosis after further work-up will not be picked up by the study.

Previous CAP studies conducted in Malaysia had approached tuberculosis very differently from one another. Liam et al excluded patients treated for pulmonary tuberculosis[27] while two other studies which did not exclude tuberculosis reported that tuberculosis as the causative pathogen in 4.8%[28] and 15.3%.[29] Although CAP is an acute respiratory infection compared to the chronic infection of pulmonary tuberculosis, it is very prevalent in our population and hence should be considered as one of the probable differential diagnosis in our approach to CAP.

In retrospect, as the clinical diagnosis of CAP is loosely defined and coupled with availability of established care pathway, CAP is a very convenient diagnosis to commit into by the front-liners upon encountering an unwell patient, with some respiratory symptoms. This practice may be acceptable as long as we were well aware of the uncertainty of CAP diagnosis and initiate further tests in wards. In the current study, we found that the mortality outcomes were statistically similar between the two groups, but the misdiagnosed patients were discharged home earlier.

There were several notable limitations in this study. Firstly, as this is a single-centred and retrospective study by design we could only collect data which were objective and available. For instance, we did not include the physical examination findings in the study. Secondly, the study was designed as an audit study hence the comparison of characteristics and outcomes were chiefly exploratory. Thirdly, there is a huge possibility that many CAP cases were not included as some were admitted to general medical, geriatrics and other medical wards. Elderly cohort patients would be a cohort with even higher prevalence of misdiagnosis.

Some outcome variables which were collected may have a variety of confounding factors. For example, the proportion of patients requiring mechanical ventilation may not be due to Community-acquired pneumonia only as nosocomial infection may be the underlying cause, as the data of duration in hospital stay prior to intubation were not collected.

Finally, and most importantly, we were relying on the clinical diagnosis and judgment of investigators to diagnose CAP based on retrospective evaluation of data, which could be flawed. For example, investigators were not able to make any alternative diagnosis in 15% of the misdiagnosis cases. Unless we can undertake a prospective study utilising the microbiological detection in the lung parenchymal, we may not be able to be entirely certain of the diagnosis. Even so, Musher et al were unable to identify a cause for CAP in 45.9% of the cases which were all being prospectively identified as infective CAP despite having advanced bacterial and viral diagnostics at their disposable.[30]

In conclusion, we had found that more than one third of our CAP patients were misdiagnosis. Although misdiagnosis of CAP in our study did not show any increase in mortality or morbidity, a proper diagnosis of CAP will be helpful in preventing inappropriate prescription of antibiotics and unnecessary admission. Also, it is most likely that a vast majority of the misdiagnosis of CAP had been made into the administrative data as CAP. This is a very important piece of information to keep in mind when we are interpreting administrative data in our policy making. In order to ascertain the findings of this study, a multi-centred, prospective, nationwide study is indicated.

ACKNOWLEDGMENT

We gratefully acknowledge the contributions of the helpful staff of the Department of Medical Records of Penang Hospital for retrieving the clinical notes and chest radiographs for the purpose of the study. Also, we would like to thank the Director General of Health Malaysia for his permission to conduct and publish the study.

FUNDING

The study received no funding.

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