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RESEARCH ARTICLE

Profile of Early Responders Versus Late Responders in Patients With Community Acquired Pneumonia an Observational Study

Dr. Sumit Khurana

National Board of Examinations

Corresponding author:
Dr. Sumit Khurana
Sumitkhurana2407@gmail.com

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ABSTRACT

Community acquired pneumonia is the most common infectious cause of mortality worldwide with India having the largest burden of the disease.1,2 Multiple criteria have been established for classification of severity and outcome assessment including the CURB-65 score and the Pneumonia Severity Index.3Recent studies like the REACH trial classified patients with CAP as early and late responders based on the HALM criteria for clinical stability and assessed various factors associated with a late response.4,7Herein, we conducted a cross-sectional study to identify factors associated with treatment response in an Indian cohort and their role in early intervention for late responders. The study shows association of late response with patient factors such as advanced age, presence of comorbidities including smoking, chronic alcohol consumption, chronic systemic illness like Chronic Kidney disease, Chronic Liver disease, diabetes Mellitus and Hypertension .Other important factors associated with inadequate or late response to treatment include high CURB-65 score at presentation, culture positivity, antibiotic modification and use of hospital resources

Keywords- : VAT, VAT Compliance and VAT Knowledge and level education.

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INTRODUCTION

Pneumonia is defined as an infection of the lung parenchyma and has a high prevalence and mortality rate in India.[3,11] Several host and microbiological agent related factors are known to effect outcomes in CAP and have been studied extensively leading to the introduction of various severity scales for early recognition and intervention for late responders. Treatment failure early during the disease course is associated with poor outcomes.[5] Various studies like the REACH analysis, Garin et al and Francisco Arancibia et al have demonstrated that various factors including patient demographics, clinical severity at presentation, investigative data including cultures, choice of initial treatment regimens and need for hospital resource use, can all be predictors of clinical response.[4,9,10] HALM criteria were initially devised by Aliberti et al to analyze the TCS and study its association with adverse outcomes including mortality.[7,12] It has since been used to classify and study patients wherein patients with a TCS of less than 4 is an early responder and those with a TCS more than or equal to 4 are late responders. These studies are based on data collected from various centers in the west and the developed world and hence we conducted a study on similar principles in an Indian cohort to define certain characteristics that are associated with late response and determine mortality related to CAP in our hospital.

MATERIALS and METHODS

The present study was conducted between December 2016 and February 2018 at Bangalore Baptist hospital. 177 patients admitted to the wards and ICU's for treatment of community acquired pneumonia and who met the inclusion criteria were enrolled in the study. 17 patients failed to achieve clinical stability and could not be included in the final analysis. The study population underwent routine clinical and investigative assessment, including change in treatment regimens, as deemed adequate by their primary treating physicians. Informed consent was taken in all cases.

INCLUSION CRITERIA

- All patients with age > 18 years
- Patients with community acquired pneumonia satisfying the case definition as specified.
- Patients requiring hospitalization for treatment.

EXCLUSION CRITERIA

- Patients with pneumonia that developed after hospitalization at health care center.
- Patients who did not give informed consent.

All patients underwent chest X-rays which were reported by a radiologist. Baseline data with regards to patient demographics, medical history, disease characteristics and clinical features was recorded. Patients were followed with once daily visits and data with regards to vitals, general condition of the patient, laboratory investigations and current treatment was recorded to ascertain microbiological diagnosis, treatment modification, clinical outcomes and use of hospital resources. Decisions regarding requirement for admission, admission to critical or non-critical area, initial antibiotic, change in antibiotic regimes and hiking up of treatment were as per the treating

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physician's discretion. Patients reaching clinical stability as per study definition were classified as early and late responders (stabilizing within 4 days were considered as early responders and those requiring 4 or more days were considered late responders). Patients who were discharged against medical advice will be excluded from the study. Data was compiled and analyzed once the study duration was completed.

HALM CRITERIA FOR CLINICAL STABILITY

- Temperature <=37.8C
- Heart rate <=100 beats/min
- Respiratory rate <=24 breaths/min
- Systolic blood pressure >=90 mm Hg
- Arterial oxygen saturation >=90% or pO2 >=60 mm Hg on room air
- Ability to maintain oral
- Normal mental status

OBSERVATIONS

Of the 160 patients who were recruited and whose data was analyzed, 82 were early responders and 78 were late responders.

Table 1 shows the association between age and time to clinical stability with the mean age of early responders being 39.62±14.406 years and for late responders was 64.12±12.669 years and this was found to be statistically significant with a p value of less than 0.001.

Table 1…. **Association of age and clinical stability**

	Responder	Total Number	Mean	Std. Deviation	P value
Age(years)	Early Responder	82	39.62	14.406	<0.001
	Late Responder	78	64.12	12.669	

Table 2 depicts association of smoking and treatment response with 49% of late responders being current smokers compared with 51% in the early responders, although the correlation was statistically significant with a p value of 0.018. Alcohol consumption was also a significant variable with 89.7% of the total 29 cases with history of chronic alcohol consumption being late responders as depicted in table 3 and the difference being statistically significant with a p value of less than 0.001

Table 2…. Association between Clinical Stability and Smoking

Smoking Status	Group	P Value

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	Early Responders (n=82) n (%)	Late Responders (n=78) n (%)	0.018
Current Smoker	25 (51.0)	24 (49.0)	
Non-Smoker	56 (56.6)	45 (43.4)	
Reformed Smoker	1 (10.0)	9 (90.0)	

Table 3…. Association of clinical stability with alcohol consumption

Alcohol Consumption	Group		P Value
	Early Responders (n=82) n (%)	Late Responders (n=78) n (%)	<0.001
Yes	3 (10.3)	26 (89.7)	
No	79 (60.3)	52 (39.7)	

Table 4 depicts the association of respiratory comorbidities with treatment response with bronchiectasis and obstructive lung disease being significantly associated with late response. Amongst cardiac comorbidities, Ischemic heart disease was significantly associated with late treatment response with 86%of the total 43 cases of known ischemic heart disease being late responders and the difference was statistically significant (figure 1). Similarly, chronic organ failures including CKD and CLD were significantly associated with late response (p value of <0.001 and 0.010 respectively) as depicted in figure 2 and 3.

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Table 4…. Association between time to clinical stability and respiratory comorbidities

Respiratory comorbidities		Group			
		Early responders(n=82) n(%)	Late responders(n=78) n(%)	Chi-square test	P value
COPD/Asthma	Yes	24 (40.0)	36 (60.0)		0.027
	No	58 (58.0)	42 (42.0)		
ILD	Yes	1 (16.7)	5 (83.3)		0.084
	No	81 (52.6)	73 (47.4)		
TB	Yes	11 (44.0)	14 (56.0)		0.430
	No	71 (52.6)	64 (47.4)		
Bronchiectasis	Yes	0 (0.0)	8 (100.0)		0.003
	No	82 (53.9)	70 (46.1)		
Other respiratory disorders	Yes	0 (0.0)	3 (100.0)		0.073
	no	82 (52.2)	75 (47.8)		

Figure 1…. Distribution of IHD in early and late responders

Figure 2…. Distribution of CKD in early and late responders

Figure 3…. Distribution of Chronic Liver disease in early and late responders

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Table 5 shows that amongst 71 patients with hypertension, 16 were early responders whereas 55 were late responders with a statistically significant difference (p value <0.001).

Hypertension	Group		P value
	Early Responders (n=82) n (%)	Late Responders (n=78) n (%)	<0.001
Yes	16 (22.5)	55 (77.5)	
No	66 (74.2)	23 (25.8)	

Table 5…. Association between Clinical Stability and Hypertension

Table 6 shows that amongst diabetics, 72.7% were late responders and the difference was significant with a p value less than 0.001.

DM	Group		P Value
	Early Responders (n=82) n (%)	Late Responders (n=78) n (%)	<0.001
Yes	18 (27.3)	48 (72.7)	
No	64 (68.1)	30 (31.9)	

Table 6…. Association between Clinical Stability and DM

Table 7…. Association of various clinical signs with TCS

Clinical signs and symptoms		Group		P value
		Early responders (n=82) n (%)	Late responders (n=78) n (%)	
Dyspnea	Yes	45 (37.5)	75 (62.5)	<0.001
	No	37 (92.5)	3 (7.5)	
Tachypnea	Yes	39 (34.2)	75 (65.8)	<0.001
	No	43 (93.5)	3 (6.5)	
Hypoxemia	Yes	18 (21.7)	65 (78.3)	<0.001

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	No	64 (83.1)	13 (16.9)	
Fever	Yes	77 (72.0)	30 (28.0)	**<0.001**
	No	5 (9.4)	48 (90.6)	
Hypothermia	Yes	0 (0.0)	4 (100.0)	0.038
	No	82 (52.6)	74 (47.4)	

Mean duration of symptoms was 3.57 days amongst early responders compared to 4.68 days amongst late responders and it was statistically significant at a p value of less than 0.001. Amongst symptoms at presentation, dyspnea, tachypnea, hypoxemia and hypothermia were more common amongst the late responders and the difference was statistically significant. Fever was more common amongst the early responders as shown in table 7.

Mean CURB-65 score at presentation was 1.15 for early responders and 2.88 for late responders (table 8) with a statistically significant p value of less than 0.001.

Table 8…. Mean CURB-65 scores in early and late responder

	Responder	**N**	**Mean**	**Std. deviation**	**P value**
CURB-65 score	**Early Responder**	82	1.15	.818	<0.001
	Late Responder	78	2.88	.837	

Culture positivity, gram positive and negative bacilli on sputum gram staining, leukocytosis and leucopenia were significant investigative differences amongst the 2 study groups as shown in figure 4 and table 9 and table 10.

Figure 4…. Distribution of Culture positive cases in early and late responders

Table 9…. Association between clinical stability and gram stain findings

Gram stain findings		**Group**		
		Early responders(n=82) n(%)	**Late responders(n=78) n(%)**	**P value**
Gram positive cocci	**Yes**	70 (54.3)	59 (45.7)	0.120
	No	12 (38.7)	19 (61.3)	
Gram positive	**Yes**	3 (15.8)	16 (84.2)	0.001
	No	79 (56.0)	62 (44.0)	

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bacilli				
Gram Negative bacilli	**Yes**	7 (14.3)	42 (85.7)	<0.001
	No	75 (67.6)	36 (32.4)	
Other/No gram stain findings	**Yes**	0 (0.0)	8 (100.0)	0.003
	No	82 (53.9)	70 (46.1)	

Table 10…. Association between Clinical Stability and WBC counts

WBC counts		**Group**		
		Early responders(n=82) n(%)	**Late responders(n=78) n(%)**	**P value**
WBC>10000	**Yes**	77 (57.0)	58 (43.0)	0.001
	No	5 (20.0)	20 (80.0)	
WBC<4500	**Yes**	1 (12.5)	7 (87.5)	0.024
	No	81 (53.3)	71 (46.7)	

Antibiotic treatment modification and rate of ICU admissions was also significantly higher amongst late responders (table 11 and 12).

Table 11…. Association between Clinical Stability and Antibiotic Modification

Antibiotic Modification	**Group**		**P value**
	Early Responders (n=82) n (%)	**Late Responders (n=78) n (%)**	<0.001
Yes	5 (8.1)	57 (91.9)	
No	77 (78.6)	21 (21.4)	

Table 12…. Association between Clinical Stability and ICU Admission

ICU Admission	**Group**		**P value**
	Early Responders (n=82) n (%)	**Late Responders (n=78) n (%)**	<0.001
Yes	9 (11.1)	72 (88.9)	
No	73 (92.4)	6 (7.6)	

Hospital resource use including mechanical ventilation, inotropic support and ARF requiring dialysis was also significantly higher amongst late responders (table 13).

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Table 13…..Association between hospital resource use and TCS

Hospital resource Use		Group		P value
		Early responders **(n=82)** **n (%)**	Late responders **(n=78)** **n (%)**	
Fluid resuscitation	Yes	1 (4.8)	20 (95.2)	**<0.001**
	No	81 (58.3)	58 (41.7)	
Inotrope use	Yes	1 (5.6)	17 (94.4)	**<0.001**
	No	81 (57.0)	61 (43.0)	
Non-Invasive Ventilation	Yes	1 (2.9)	34 (97.1)	**<0.001**
	No	81 (64.8)	44 (35.2)	
Invasive Ventilation	**Yes**	1 (6.7)	14 (93.3)	**<0.001**
	No	81 (55.9)	64 (44.1)	
ARF Requiring Dialysis	Yes	1 (12.5)	7 (87.5)	0.024
	No	81 (53.3)	71 (46.7)	

The overall mortality observed in our study was 9.6% as shown by figure 5.

Figure 5…. Mortality amongst study population

DISCUSSION

Patients included in our study underwent evaluation at presentation and were later followed up and divided according to their TCS into early and late responders. Our results highlighted the benefits of identifying patients with CAP and in identifying patients who are at a higher risk of late response and assist clinicians in risk stratification and early intervention.

With regards to demographics, age at presentation was a significant factor in terms of TCS as most of the patients under 50 years of age were early responders and this trend saw a shift towards late response with advanced age in late responders in which group more than 80% of patients were above 60 years' age. This contrasts with the REACH analysis where mean age of early responders was comparable to that of late responders.

The percentage of late responders was particularly high in reformed smokers while current smokers had similar outcomes numerically in each group. There was an increased risk of poor outcome in patients who are either current or reformed smokers. Our study also showed and increased percentage of reformed smokers with CAP which represents increased risk of infection with chronic smoking but does not clearly predict treatment response outcomes.

Alcohol consumption was demonstrated in various studies to be a significant risk factor for CAP and was also shown to be associated with treatment failure. Our study similarly demonstrates increased risk of late response to treatment in patients with history of chronic alcohol consumption.

REACH analysis showed that about 14.5% of early responders and 20.5% of late

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responders had a history of congestive cardiac failure suggesting poor outcome with severe cardiovascular morbidities. Our study similarly establishes a significant association between IHD and late response to treatment amongst patients with CAP.

There is a paucity of large studies regarding association of CKD and Diabetic Nephropathy with response to treatment in CAP, but mortality increases 14 to 16 folds in patients who have ESRD. Our study demonstrates that 89.7% of patients with documented CKD were late responders. All patients who had Chronic Liver disease at presentation were part of late responders in our study and various other research has increased incidence of CAP and increased risk of mortality in patients with CLD.

Diabetes Mellitus and Hypertension were also more commonly seen in late responders in our study and the differences were statistically significant. This was in contrast to the REACH analysis where numerically similar patients in each group had diabetes. Studies with regards to association of Hypertension with outcomes in CAP are lacking.

Disease Characteristics that were significantly associated with the TCS in determining response to treatment were duration of symptoms, Fever, dyspnea, tachypnoea, hypoxemia and hypothermia at presentation. These characteristics were part of the REACH analysis but did not demonstrate any statistically significant difference with regards to outcomes, in contrast to our study. In the REACH analysis 58% of patients who presented with fever were early responders which again is statistically different from our finding where fever at presentation showed good outcome. The mean duration of symptoms at presentation was lower in early responders compared to late responders.

All patients with a CURB-65 score of more than or equal to 4 were late responders with similar findings reported in the REACH analysis where 30 out of 56 patients with a score more than 4 were late responders and this is in keeping with the consensus that later responders tend have higher severity scores at presentation.

All patients underwent radiological investigations with one patient undergoing addition CECT of the chest for diagnostic purposes. Early responders (58.4%) tended to have more of consolidation on x-rays compared to late responders (41.6%). In the REACH analysis, 52% patients who had consolidation were early responders and 48% were late responders. These figures are like our study and are statistically significant.

Culture positivity was more common in late responders compared to early responders with MSSA being the most common organism isolated followed by Klebsiella and streptococcus Pneumoniae. Gram stains were obtained on sputum and or ET tube secretions and late responders were more likely to have gram positive bacilli, gram negative bacilli and no/other gram stain findings as compared to early responders. Other studies regarding association of gram staining with outcomes are lacking.

Leukocytosis on initial evaluation was associated with good response as seen in our study. 57% of patients with a WBC count more than 10000 were early responders compared to 43% late responders and the difference was statistically significant. This is likely to represent good initial immune response to the infection. Patients with leukopenia had a poorer response as patients with WBC counts less than 4500 were more

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commonly late responders (87.5%) compared to early responders (12.5%). This includes patients who had severe sepsis at presentation and were likely immunocompromised owing to underlying comorbidities. The differences in this group were also statistically significant. These findings are in keeping with other studies, although research comparing impact of WBC counts on time to clinical stability is lacking.

Both groups of patients were treated according to hospital protocols with the treating clinician's discretion considered at the time of admission with regards to initial antibiotic used. All patients who were included in the study were started on parenteral antibiotics. Most commonly used combination was a cephalosporin and macrolide with 84 out of 160 patients initiated on ceftriaxone and azithromycin. Within this group 72(85.7%) were early responders and 12(14.3%) were late responders. Out of 65 patients treated with a broader spectrum antibiotic combination of piperacillin/tazobactam and azithromycin, 7.7% were early responders while 92.3% were late responders. Such differences likely represent the decision of the admitting or treating physician wherein patients with higher comorbidities and poorer initial assessment scores, were initiated on higher end antibiotics. In our study early responders were more likely to receive initial antibiotics as per established protocols than were late responders, in whom, early escalation of antibiotics was considered as per the treating clinician's judgement.

Antibiotic modification was also less likely in early responders compared to late responders based on treatment response and sensitivity patterns. The above difference in patterns of antibiotic modification may represent discrepancies in initial treatment choices or increased virulence and resistance of infecting organisms in late responders. Antibiotic modification in REACH analysis was seen in 34.8% of early responders compared to 65.2% in late responders. These figures agree with our study as to higher incidence of treatment failure requiring escalation of treatment in late responders.

In terms of association of hospital resource use and treatment response, there was a clear tendency towards late response in patients who were admitted to the ICU initially, who required fluid resuscitation and or inotropic support for septic shock and those who underwent hemodialysis for sepsis related ARF. Similar results were obtained in REACH analysis. Data regarding incidence of transfer to ICU or requirement of inotropes after initial evaluation and achieving clinical stability owing to acute clinical events is lacking in our study. Similarly, duration of hospital stays or duration in the ICU was not assessed since these variables could not be assessed before and after clinical stability. Use of mechanical ventilation at presentation for indications including respiratory failure, low GCS, septic encephalopathy or cardiorespiratory collapse was associated with poor response in our study. Owing to lack of data specified earlier, patients requiring ventilation later during hospitalization after classification as early or late responders, is lacking. The secondary outcome of our study was to determine the mortality in patients with CAP. Out of 177 patients initially recruited to the study, 17 died and thus did not fit criteria of early or late responders owing to lack of clinical response as assessed by daily HALM criteria assessment. In our study, all patients who died did not fulfil the HALM criteria on any given day of assessment and thus were not

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included in either group. The mortality rate varies amongst various studies and was 9.6% in our study

CONCLUSION

Community acquired pneumonia is a common infectious condition which requires adequate initial assessment, stratification and treatment to prevent excessive morbidity due to prolonged illness and its complications. Our study was designed to identify factors that can help the treating physician in early identification of patients who may require intensive care and are at risk of treatment failure. The patient and disease characteristics, clinical outcomes and hospital resource use were analyzed according to the TCS of patients using the Halm's criteria.

The study demonstrates certain demographic differences in terms of age in both the study groups, but no significant association was seen with gender. Patients with more comorbidities at presentation, particularly Diabetes, hypertension, history of smoking, chronic alcohol consumption, chronic liver disease, Chronic kidney disease and diabetic nephropathy were more likely to be late responders. Initial scoring by CURB-65 showed a significant association between higher scores and poor clinical response.

In contrast to other studies, our study demonstrated significant association between disease characteristics at presentation and response to treatment. These included symptoms such as dyspnea at presentation and signs such as fever, tachypnoea, hypoxemia and hypothermia. Thus, identification of clinically unstable patients at presentation and timely escalation of treatment to improve response to treatment is required.

Higher number of gram negative and culture negative cases amongst late responders suggests increased virulence of these organisms and early escalation of antibiotics is recommended in such cases.

The choice of initial antibiotic was as per the hospital guidelines and the treating clinician's discretion and there was a tendency for late responders to receive broader spectrum antibiotics as initial treatment. Also, later response was more likely associated with treatment modification which suggests that early recognition of such patients may help reduce patient and hospital burden in terms of length of stay and costs incurred.

Higher chances of ICU admissions, therapy for shock, multi-organ failure with ARF requiring hemodialysis and requirement for mechanical ventilation were seen in late responders. This demonstrates the importance of early recognition of such patients to improve outcomes and reduce burden on hospital resources with additional benefits of earlier treatment de-escalation and discharge.

The limitations of the study include the small number of patients in the study population, lack of data regarding in-hospital deterioration and escalation or de-escalation of treatment in each patient, lack of subsequent follow up data in terms of post stability outcomes.

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