

The Direct Economic Disease Burden of Healthcare-associated Infections (HAIS) and Antimicrobial Resistance (AMR): A Preliminary Study in a Teaching Hospital of Nepal

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Research

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Abstract

Background: Healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) have been becoming the public and global health issues. The purpose of this study is to estimate the direct economic burden attributable to HAIs and AMR.

Methods: This study applied propensity score matching (PSM) methodology to conduct a prospective case-control study of direct disease burden attributable to HAIs and AMR 16th December, 2017 to 16th April, 2018 in a teaching hospital in Nepal. Clinical information was retrieved from Hospital Health Information and electronic medical record systems, as well as the microbiology lab system. The finance system was used to determine the health expenditure and length of hospitalization of HAIs, HAIs-AMR and Non-HAIs patients. STATA 12.0 was used to conduct descriptive analysis, (bivariate) χ^2 test, paired/independent *T* test, PSM (B=0.25a, nearest neighbour 1:1 matching, General Boosted Model, GBM). The statistically significant level was set at $P < 0.05$.

Results: HAIs patients and HAIs-AMR patients had statistically significant higher expenditures and longer length of hospital days than Non-HAI inpatients during the study period ($P < 0.05$). The additional average total medical expenditure, medicines expenditure, out-of-pocket expenditure and length of hospitalization per patient caused by HAIs were 17,224.93 Rupees, 11,947.49 Rupees, 15,776.57 Rupees and 7 days, respectively. In the meantime, the extra total medical expenditure, medicines expenditure, out-of-pocket expenditure and length of hospitalization attributable to HAIs-AMR were 39,879.63 Rupees, 21,173.63 Rupees, 38,770.87 Rupees and 9 days, respectively. Moreover, the percentage of out-of-pocket expenditure accounting for total medical expenditure of HAIs Group was 94.24% while it was 96.75% of HAIs-AMR Group.

Conclusions: It was the first time to apply the research framework of the previous study in China to estimate the direct economic burden caused by HAIs and AMR in a teaching hospital of Nepal. HAIs and AMR have substantially led to excess direct economic burden for patients and their family due to the low Gross Domestic Product (GDP) and low health expenditure in Nepal. This calls for active collaboration with developed countries to reduce the threat caused by HAIs and AMR to prevent the transnational communication.

Introduction

Healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) have been becoming the public and global health issues, which have a great impact on patients' safety (1-4). Both of them are associated with increasing mortality, morbidity and length of hospitalization (5). Eventually, there is an increasing economic burden on society, patients and their family (6-8). In the United States, the annual approximate number of deaths caused by HAIs was 90,000 from 1990 to 2002, corresponding to US\$ 28 to US\$ 45 billion per year (9). The worldwide estimated annual mortality attributable to AMR was 700,000 in 2014 (10). And if there is still no any action to be taken to address AMR, the deaths could be around 10 million in 2050, resulting in a reduction of 2% to 3.5% in Gross Domestic Product (GDP) and the economic loss being US\$ 100 trillion (10). However, there is no such study to show the level of economic loss caused by HAIs and AMR in Nepal after searching main online databases, including MEDLINE, EMBASE and PubMed. Just one unpublished study showed the overall point prevalence of HAIs in a teaching hospital of Nepal was 2.4% in 2001 without any details (11), which was much lower than that in developing countries (15.5%) reported by Allegranzi team in 2010 (3).

It is the first time to apply our research team's previous estimation framework to estimate the economic burden due to HAIs and AMR in a teaching hospital of Nepal. The framework was designed to calculate the direct economic burden attributable to HAIs and AMR in Hubei Province, China given the support from the UK (6). The idea was put forward because of the 'One Belt, One Road' initiative proposed by Chinese President Xi in 2013, aiming to improve cooperative relationship with countries included in this initiative (12). Furthermore, China and Nepal signed a Memorandum of Understanding (MoU) due to the initiative in 2017 (13). Health cooperation is one of the key issues and realises China's commitment to the establishment of mutual relationship.

At the same time, AMR has been always the main health issue. In May 2015, World Health Organization (WHO) passed a global action plan against AMR in the 68th World Health Assembly and called on a national action plan in each Member States (14). Besides, it is the first time for world leaders to put tackling AMR into their national affairs at the G20 summit held in Hangzhou, China in 2016 (15). It is also recognized that AMR could lead to a reduction on global economic productivity (15). In Nepal, irrational use of antibiotics is a serious problem. Patients get unlimited access to antibiotics in hospitals or pharmacy, while clinical doctors give prescriptions without strict regulation.

Based on the above-mentioned background, quantifying the direct economic burden caused by HAIs and AMR in Nepal is not just a kind of cooperation between China and Nepal, but also could help policy-makers and hospital managers to set HAIs and AMR as priorities. The purpose of this study is to estimate the direct economic burden attributable to HAIs and AMR by comparing the differences of health expenditures and length of hospitalization between patients with HAIs vs. patients without HAIs and patients with HAIs and AMR vs. patients without HAIs in a teaching hospital of Nepal.

Methods

Study design

According to previous research in Hubei Province of China, in order to estimate the direct economic burden caused by HAIs and AMR, there were two case-control groups to compare the health expenditure and the length of hospitalization. Specifically, the first group was the patients with HAIs (HAIs Group) vs. the patients without HAIs (Non-HAIs Group) while the other group was the patients with antimicrobial resistant HAIs (HAIs-AMR Group) vs. the patients without HAIs (Non-HAIs Group). Before conducting the comparisons, there was a need to control the characteristics between the case group and the control group. Propensity Scoring Matching (PSM) (16) method was applied to randomly assign the patients into the case-control groups by matching a set of covariates (gender, age, diagnosis, incubation and surgery) like a random clinical trial (RCT).

Settings

A prospective study was conducted from 16th December, 2017 to 16th April, 2018 in a teaching hospital in Nepal.

Participants

All inward patients, except new-born patients and patients from neonate intensive care unit (NICU), were selected for a prospective review by a group of trained investigators during study period. Patients discharged on the 16th April, 2018 were included and patients admitted on the same date were excluded.

Inclusion criteria

1) Patients admitted to the hospital were more than 48 hours; 2) Patients were more than one year old; 3) Patients had necessary information regarding demographic and sociological information and diagnosis; 4) Patients' expenses data were kept in the hospital database and complete.

HAls group

1. Patients met the criteria defined by Europe Centres for Disease Control and Prevention (ECDC) (17) for HAls.
2. Positive findings of microbiological culture tests can be found from the microbiology lab or based on the clinical experience.
3. Patients did not have any kind of infection at the time of admission.

HAls-AMR group

1. Patients met the criteria for HAls patients.
2. Positive findings of antimicrobial resistant bacteria of microbiological culture test from the microbiology lab.

Non-HAls group

1. Patients were not diagnosed with community acquired infections and did not have any kind of infection at the time of admission.
2. Negative findings of microbiological culture test were found from the microbiology lab.

Exclusion criteria

General exclusion criteria were as follows: 1) the period for admission was less than 48 hours; 2) patients did not have full demographic and sociological information and diagnosis; 3) patients' expenses data were incomplete; 4) patients were less than one year old.

HAls group

1. Patients did not meet the criteria defined by ECDC for healthcare-associated infections.
2. Negative findings of microbiological culture test were found from the microbiology lab.
3. Patients were diagnosed with community acquired infections and had infection at the time of admission.
4. Patients had secondary infections (infections that occurred during or after treatment for another infection.).

HAls-AMR group

1. Exclusion criteria for HAls group were suitable for HAls-AMR patients.
2. Negative findings for antimicrobial resistant bacteria of microbiological culture test were found from the microbiology lab.

Non-HAls group

1. Patients were diagnosed as HAls or community acquired infections.
2. Patients had any other kind of infections at the time of admission.

Variables

The set of matching conditions (gender, age, diagnosis, incubation and surgery) was chosen based on the previous study (6) and current literature. The total medical expenditure, medicines expenditure, out-of-pocket expenditure (some patients can get some reimbursement from the teaching hospital, so that patients can just pay only part of the bills.) and the length of hospitalization were compared between the two matched groups with similar observable variables regarded as the outcome of the direct economic burden.

Data sources

The demographic information of patients was extracted from the Hospital Information System (HIS) of the study hospital. The clinical information was retrieved from the HIS, the electronic medical record system and the microbiology lab system. Health expenditure and hospitalization length data were extracted from the hospital finance system. Data collectors were trained with the uniformed survey procedures and the inclusion and exclusion criteria. Quality control was realized by routine meetings and second data verification.

Bias

Regarding to the comparison between the HAIs-AMR patients and the Non-HAIs patients, ideally, the HAIs-AMR patients should be compared with the HAIs patients without antimicrobial resistant bacteria (control group) to estimate the direct economic burden attributable to AMR. The preconditions for conducting PSM method is the number of HAIs patients without antimicrobial resistant bacteria (control group) should be at least 10 times higher than the number of HAIs-AMR patients (case group) (18). However, in this study, the ratio of HAIs-AMR patients of the overall HAIs patients was more than 60%, thereby there being not enough HAIs patients without antimicrobial resistant bacteria to implement the PSM method.

Statistical methods

STATA 12.0 version was employed to conduct the following statistical analysis: 1) (bivariate) test on the difference of gender, incubation and surgery distribution; 2) (bivariate) *T* test on the differences of age and diagnosis distribution before and after PSM method to test the comparability between the case and control groups; 3) using gender, age, diagnosis code, incubation and surgery as matching conditions to perform PSM analysis between the two comparison groups ($\lambda = 0.25$, nearest neighbor 1:1 matching, without replica, Generalized Boosted Modelling, GBM) (19); 4) *T* test on the differences of health expenditures and length of hospitalization between the case and control groups to estimate the direct economic burden attributable to HAIs and AMR.

Results

General information of included inward patients

According to the inclusion and exclusion criteria, a total of 2,298 episodes of inward patients were included in this study. Specifically, there were 76 episodes of inward patients with HAIs while 46 episodes of them were diagnosed with AMR. The episodes of inward patients without HAIs were 1,904. Besides, there were a total of 318 episodes of patients diagnosed as community acquired infections. The prevalence of HAIs was 3.31% during the study period.

Comparison of covariates between HAIs Group vs. Non-HAIs Group and HAIs-AMR Group vs. Non-HAIs Group before performing PSM analysis

As Table 1 and 2 show, there were significant statistical differences of diagnosis code, incubation and surgery between HAIs Group vs. Non-HAIs Group and HAIs-AMR Group vs. Non-HAIs Group ($P < 0.05$). However, there were no significant statistical difference of gender and age between the two comparison groups ($P > 0.05$). It can indicate that direct comparison between the two comparison groups to estimate the direct economic burden was not appropriated because of the unbalanced covariates.

Comparison of covariates between HAIs Group vs. Non-HAIs Group and HAIs-AMR Group vs. Non-HAIs Group after performing PSM analysis

After conducting PSM method between the two comparison groups, there were no significant statistical differences of all the covariates ($P > 0.05$) based on Table 3 and 4. Further, regarding to HAIs Group vs. Non-HAIs Group, the number of matched pairs was 66 while it was 35 for HAIs-AMR Group vs. Non-HAIs Group.

Direct economic disease burden attributable to HAIs and AMR after performing PSM analysis

As is shown in Table 5, the excess total medical expenditure, medicines expenditure, out-of-pocket expenditure and length of hospitalization caused by HAIs were 17,224.93 Rupees, 11,947.49 Rupees, 15,776.57 Rupees and 7 days, respectively ($P < 0.05$). In the meantime, the extra total medical expenditure, medicines expenditure, out-of-pocket expenditure and length of hospitalization attributable to HAIs-AMR were 39,879.63 Rupees, 21,173.63 Rupees, 38,770.87 Rupees and 9 days, respectively ($P < 0.05$) (See Table 6). Moreover, the percentage of out-of-pocket expenditure accounting for total medical expenditure of HAIs Group was 94.24% while it was 96.75% of HAIs-AMR Group.

Discussion

In this study, we found that the prevalence of HAIs in the teaching hospital was low (3.31%). It was calculated by episodes of patients with HAIs accounting for episodes of total of patients admitted to the teaching hospital. It was much lower than that in developing countries reported by Allegranzi team in 2010 (15.5%) (3) in a systematic review and meta-analysis. It was even much lower than that in developed countries reported by WHO in 2011 (7.6 per 100 patients) (20). Compared with the prevalence of HAIs on point prevalence survey days of five public tertiary hospitals gotten in our team's previous research in Hubei Province, China (2013-2015: 2.69%) (6), it is slightly higher. It is mainly because of the different methods to conduct the HAIs and AMR prevalence survey. In this teaching hospital, there is a department named Infection Control Centre (ICC). However, it is not a routine job for the department to carry out inspection of HAIs and AMR. This was the first time to undertake such a survey by cooperating with the health professionals of the teaching hospital. Based on the experience on our previous research in China, a new survey table was designed but the identification of HAIs and AMR was defined by European Centre for Disease Control and Prevention (ECDC). Therefore, the number of patients diagnosed as HAIs and AMR may be lower than the actual number thereby a low prevalence. It may be also because of the limited health resources in the teaching hospital. The main investigators were nurses and staff from the microbiology lab in this study. It means a lack of support was available from clinical doctors. This could result in a low number of patients with HAIs and AMR. Because when a patient should be diagnosed as HAIs, the patient was assigned to the Non-HAIs group in our practice.

Usually, HAIs and AMR are related to a weak healthcare system. Poor infection control is the key driver of HAIs. However, there is no establishment of HAIs and AMR surveillance systems in Nepal, which could help the hospitals to monitor, alert and analyse HAIs and AMR cases according to the evidence from the developed countries, like the United States (21), European Countries (22-24) and the United Kingdom (25-27). Health professionals might not be willing to report

HAIs without incentives. Such low reporting might lead to even more serious and broader infections, deteriorate the infection control, and make the situations complex. Given these factors, hospital management rules might likely restrain active reporting of HAIs.

This study showed that the extra total medical expenditure, medicines expenditure, out-of-pocket expenditure and length of hospitalization caused by HAIs were 17,224.93 Rupees, 11,947.49 Rupees, 15,776.57 Rupees and 7 days. The conclusion that HAIs can increase the direct economic burden from the patient perspective is consistent with other international studies. With a foreign currency exchange by using the rate (109.70) in 25th August 2019 published by Nepal Bank Limited, the respective extra total medical expenditure, medicines expenditure, and out-of-pocket expenditure caused by HAIs were US\$ 157.02, US\$ 108.91 and US\$ 143.82. Compared with the results calculated in Hubei province, China (the respective values were 6,173.02 US\$, 2,257.98 US\$ and 1,958.25 US\$), the direct economic burden caused by HAIs was much lower. It cannot be said that the issues of HAIs should not be set priority when it comes to talk about the gross domestic product (GDP) and health expenditure in Nepal. By the end of 2018, Nepal's GDP was US\$ 28.81 billion, ranking 107th in the world and its gross domestic product per capita was US\$ 812.20 (28). Nepal's total per capita health expenditure in 2014 was US\$ 54, and health expenditure accounted for 5.8% of GDP (29). HAIs indeed have increased the financial burden for the patients and their family.

This study also found that the excess total medical expenditure, medicines expenditure, out-of-pocket expenditure and length of hospitalization attributable to HAIs and AMR were 39,879.63 Rupees, 21,173.63 Rupees, 38,770.87 Rupees and 9 days, respectively. Though the direct economic burden attributable to AMR cannot be calculated by comparing the differences between HAIs Group vs. Non-HAIs Group and HAIs-AMR Group vs. Non-HAIs Group, it does indirectly indicate AMR has further increased the direct economic burden for the patients. This is because of irrational use of antibiotics. And the main reason why irrational use of antibiotics existed in this hospital is that clinical doctors lack the awareness of regulation of AMR when giving prescriptions to patients. It is also because patients' access to buying antibiotics is not limited to hospitals and pharmacies, which further has aggravated the situation, though the government of Nepal has promulgated several policies to regulate antibiotics use since 2014 (30). Therefore, this calls for training for hospital staff and the public to increase their awareness of AMR. In hospitals, clinical staff's performances should be related to their prescription behaviour.

This study also showed that the percentage of out-of-pocket expenditure accounting for total medical expenditure of HAIs Group was 94.24% while it was 96.75% of HAIs-AMR Group. It means patients have a high economic pressure to pay the medical expenditure. In the teaching hospital, only the staff and their family can get free healthcare due to welfare provided by the hospital. Even if some patients can get some reduction for the expenditure because of charity, the rate is low. The lack of access to health insurance in Nepal is the main reason to result in high financial burden for the patients. Actually, in 2013, Nepal published the National Health Insurance Policy. However, this policy was not carried out properly because of financing (31). This means Nepal needs to take more powerful actions to forward accomplish a universal healthcare insurance to reduce the disease burden for patients.

All above-mentioned problems are associated with an uncompleted hospital information system in the teaching hospital of Nepal. In this teaching hospital, Midas is mainly adopted as the hospital information system. The main function of Midas includes financial system and details of treatment and general information of patients. The main weakness of Midas is that it is not able to synchronize the information among the sub systems though the information from different sub systems can be shared. Specifically, the practice of an electronic medical record has been not achieved. Once there was difference of the information gotten from Midas and the paper medical records, the information of the medical records was more reliable. Another problem was about the financial system. Actually, it was not direct to get the total medical expenditure from Midas. The list of all kinds of expenditure was split into two sub systems. Without synchronization, the total medical expenditure was needed to be calculated again, causing inconvenience for the researchers.

Strengths and Limitations

Compared with the manual matching, this study used a more reasonable approach (PSM) to select the balanced case and control groups to estimate the economic burden attributable to HAIs and AMR. And this is the first time to conduct such a research of HAIs and AMR in this hospital of Nepal by international collaboration. However, there are still some limitations. First, the study period was short, thereby not getting an enough number of patients to estimate the direct economic burden only attributable to AMR. It is better to continue such study in several years to get a more robust result. Second, this study focused on a single-centre hospital. It will be better to extend the research to several hospitals in Nepal to estimate the direct economic burden caused by HAIs and AMR at a national level.

Conclusion

It was the first time to apply the research framework of the previous study in China to estimate the direct economic burden caused by HAIs and AMR in a teaching hospital of Nepal. HAIs and AMR have substantially led to excess direct economic burden for patients and their family due to the low GDP and low health expenditure in Nepal. More powerful policies and guidance should be formulated to limit the access to antibiotics. Also, the awareness of hospital staff and the public should be improved. Active collaboration with developed countries should be called for to reduce the threat caused by HAIs and AMR to prevent the transnational communication.

Abbreviations

HAIs: Healthcare-Associated Infections

AMR: Antimicrobial Resistance

GBM: General Boosted Model

GDP: Gross Domestic Product

MoU: Memorandum of Understanding

WHO: World Health Organization

RCT: Random Clinical Trial

NICU: Neonate Intensive Care Unit

ECDC: Europe Centres for Disease Control and Prevention

HIS: Hospital Information System

ICC: Infection Control Centre

Declarations

Ethics approval and consent to participate

The research protocol was approved by the Institutional Review Committee School of Medical Science/Dhulikhel Hospital (IRC-KUSMS) and the number is 128/17.

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the authors upon reasonable request and with permission of Dhulikhel Hospital.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

R.S. and H.L. designed the framework of the paper. X.L. collected the data, performed the data analysis and wrote the draft paper under the supervision of R.S. and H.L. P.K., B.M. and P.T. collected the data.

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Tables

Table 1 Comparison of covariates of HAIs and Non-HAIs groups before performing PSM analysis

Covariates		HAI Group	Non-HAI Group	χ^2	P	T	P
		N (%)					
Gender	Male	38(50.67)	817(42.91)	1.769	0.183	-	-
	Female	37(49.33)	1,087(57.09)				
Age		42±18	40±20	-	-	0.998	0.318
Diagnosis code		-	-	0.006*	-	-	-
Incubation	Yes	35(36.67)	323(16.96)	42.963	<0.001	-	-
	No	40(63.33)	1,581(83.04)				
Surgery	Yes	57(76.00)	1,050(55.15)	12.730	<0.001	-	-
	No	18(24.00)	854(44.85)				

* Fisher's exact test. There is no list of diagnosis code frequency considering it is too much (more than 20 categories).

Table 2 Comparison of covariates of HAIs-AMR and Non-HAIs groups before performing PSM analysis

Covariates		HAI-AMR Group	Non-HAI Group	χ^2	P	T	P
		N (%)					
Gender	Male	23(51.11)	817(42.91)	1.206	0.272	-	-
	Female	22(48.89)	1,087(57.09)				
Age		45±20	40±20	-	-	1.707	0.088
Diagnosis code		-	-	0.044*	-	-	-
Incubation	Yes	28(62.22)	323(16.96)	60.981	<0.001	-	-
	No	17(37.78)	1,581(83.04)				
Surgery	Yes	33(73.33)	1,050(55.15)	5.889	0.015	-	-
	No	12(26.67)	854(44.85)				

* Fisher's exact test. There is no list of diagnosis code frequency considering it is too much (more than 20 categories).

Table 3 Comparison of covariates of HAIs and Non-HAIs groups after performing PSM analysis

Covariates		HAI Group	Non-HAI Group	χ^2	P	T	P
		N (%)					
Gender	Male	34(51.52)	41(62.12)	1.513	0.219	-	-
	Female	32(48.48)	25(37.88)				
Age		46±23	42±18	-	-	1.378	0.173
Diagnosis code		-	-	0.256	-	-	-
Incubation	Yes	34(51.52)	37(56.06)	0.274	0.600	-	-
	No	32(48.48)	29(43.94)				
Surgery	Yes	49(74.24)	46(69.70)	0.338	0.561	-	-
	No	17(25.76)	20(30.30)				

* Fisher's exact test. There is no list of diagnosis code frequency considering it is too much (more than 20 categories).

Table 4 Comparison of gender, age, diagnosis code, incubation and surgery of HAIs-AMR and Non-HAIs groups after performing PSM analysis

Covariates	HAIs-AMR Group		Non-HAIs Group	χ^2	P	T	P
	N (%)						
Gender	Male	18(51.43)	25(71.43)	2.954	0.086	-	-
	Female	17(48.57)	10(28.57)				
Age		46±18	45±20	-	-	0.033	0.974
Diagnosis code		-	-	0.721	-	-	-
Incubation	Yes	21(60.00)	25(71.43)	1.014	0.314	-	-
	No	14(40.00)	10(28.57)				
Surgery	Yes	26(74.29)	24(68.57)	0.280	0.597	-	-
	No	9(25.71)	11(31.43)				

* Fisher's exact test. There is no list of diagnosis code frequency considering it is too much (more than 20 categories).

Table 5 Direct economic burden attributable to HAIs after performing PSM analysis (Rupees, Days)

Disease Burden Indicators	HAIs Group	Non-HAIs Group	Differences	Standard Error	T	P
T**		57,322.30±55,072.98	40,097.37±47,842.21			17,224.93±68,515.17 8,433.64
M**	24,675.39±27,729.56	12,727.90±21,422.38	11,947.49±34,089.52	4,196.13	2.847	0.006
O**	54,023.36±54,686.43	38,246.80±47,432.64	15,776.57±68,110.00	8,383.76	1.882	0.064
L**	14±10	7±4	7±10	1	5.404	<0.001

**T= Total Expenditure per Inpatient; M= Medicines Expenditure per Inpatient; O= Out-of-Pocket Expenditure per Inpatient; L= Length of Hospital Stay per Inpatient

Table 6 Direct economic burden attributable to HAIs with AMR after performing PSM analysis (Rupees, Days)

Disease Burden Indicators	HAIs-AMR Group	Non-HAIs Group	Differences	Standard Error	T	P
T**		74,242.87±65,591.30	34,363.24±39,857.72			39,879.63±79,079.82 13,366.93
M**	34,577.15±33,709.60	13,403.52±23,817.41	21,173.63±41,228.42	6,968.88	3.038	0.005
O**	71,833.35±64,609.18	33,062.48±39,076.55	38,770.87±68,110.00	13,029.76	2.976	0.005
L**	16±11	7±7	9±11	2	4.493	<0.001

**T= Total Expenditure per Inpatient; M= Medicines Expenditure per Inpatient; O= Out-of-Pocket Expenditure per Inpatient; L= Length of Hospital Stay per Inpatient