statements, material costs, rental costs, and depreciation. Figure 1 shows an example of the calculation method of this new costing system. In the case of personnel costs or salary, total salaries were subdivided first by individual staff, then by the various services provided, before linking the services to patients via patient-oriented tracing. Finally, these costs were then calculated at the individual patient level. Similarly, in the case of material goods provided, the costs of these materials were categorized by health services function, and these functions linked to individual patient costs via patient-oriented tracing.

Practical Application of the New Costing System

We then applied this new costing system to the calculation of patient-level costs in two voluntary participant acute care hospitals. Patient-level costs per day were calculated with the cooperation of the staff from these hospitals, and feedback was obtained from the staff with regard to the usability and practical application of the system.

RESULTS

Database

Our database comprised of data from 284 730 patients and individual patient case-level costs with components. For the model, we used an exchange rate of 110 Japanese yen (JPY) = US$1. A wide range of average costs per hospitalization, from $820 to $65 737 ($Q_1$: $4 373;

Q_2: \$7 163; Q_3: \$12 712) was observed. Average costs per diem varied from \$300 to \$2 475 (Q_1: \$437; Q_2: \$491; Q_3: \$565) .

The costs of materials for inpatients within the Major Diagnostic Category (MDC) of MDC05 (diseases/disorders of the circulatory system) and MDC13 (diseases/disorders of the blood and blood-forming organs and immunological disorders) comprised a large portion of the total cost, when compared with costs of materials for inpatients with other MDCs. Inpatients who had undergone surgery had a higher cost per diem than that of non-surgical inpatients within any MDC. Moreover, the cost of materials in hospitalizations involving surgery and the percentage of the cost of materials as a component of total cost were higher than for non-surgical inpatients in almost all MDCs. In contrast, the cost of materials was higher, and the cost of materials represented a higher proportion of total cost in non-surgical inpatients in the following MDCs: MDC08, MDC09 (diseases/disorders of the breast), MDC11 (diseases/disorders of the kidney, urinary tract and male reproductive system) and MDC12 (diseases/disorders of the female reproductive system) compared with the cost of materials in surgical inpatients with the same MDCs. A high correlation (correlation coefficient = 0.94) between costs and charges was observed. Figure 2 shows a graph sample of the total and component costs of angina patients of selected hospitals for a multi-institutional comparison. The results show that there was considerable variation in costs even in the treatment of an identical disease.

New Patient-Oriented Costing System Using Function Tracing

The new costing system utilizes two methods of assignment costs to cost object: direct tracing and tracing by function drivers. Of the two methods, direct tracing is the most precise because it relies on physically-observable causal relationships. Driver tracing, which is ostensibly less accurate than direct tracing, relies on causal factors known as drivers to assign costs to cost objects (for each patient). Traditional methods of cost calculation have difficulties in the identification and tracking of resources to individual patients. In contrast, the use of driver tracing can in principle identify all resources used by a patient, and the associated costs can therefore be calculated. Based on this principle, all costs of resources of hospitals are apportioned according to the Mutually Exclusive and Collectively Exhaustive (MECE) principle into patient-oriented functions. A function definition database was prepared, and measurements for utilization were calculated for each function according to this list. This function definition database was then used to assign costs of each function to cost objects for individual patients.

Figure 3 shows the model of the patient-oriented costing system using function tracing.

The patent of this New Patient-Oriented Costing System was applied in March, 2006 and patented by Japan Patent Office [11].

Practical Application of the New Costing System

The new costing system was applied to calculating patient-level costs in two hospitals. Figure 4 shows an example of the differences in mean patient-level costs and cost components per day for several patients with pneumonia using this new system. It was observed that even among patients with an identical disease, there was a large degree of variation in these costs. Figure 5 shows the details of patient-level mean costs and hospital income. Again, the results show a large degree of variations in patients with an identical condition (pneumonia), with regard to costs and hospital income, as well as the ensuing profit from each patient.

By using the costing data from all patients, we are able to calculate the total hospital costs and cost components by the various MDCs, as shown in Figure 6. (Note: MDC2 was excluded from this Figure as the participating hospital that provided the data for this calculation did not have any patients within this category).

Discussions with the study hospitals after the calculation analysis showed that the hospital staff were appreciative of the increase in accuracy in patient-level costing, as well as the decrease in labor-intensiveness in the calculation process.

DISCUSSION

In this study, we have developed a multi-institutional costing database comprising of data from 284 730 patients. We then developed a new patient-level costing system based on function

tracing using this database. Finally, we applied the new costing system into calculating health care costs for patients in two hospitals.

Advantages of the New Costing System

Our study has several advantages over existing traditional methods. First, the new system can improve the accuracy of patient-level costing. Second, the new system substantially reduces the time and effort required for data preparation and cost calculation. Although traditional methods are limited in the identification of specific resources used by individual patients, our use of driver tracing techniques has allowed all resources used to be apportioned into patient-oriented functions according to the MECE principle. The function definition database allows quick identification of the resources used and costs incurred by individual patient.

Difference between new costing system and traditional costing system

Figure 5 shows the main differences between our new costing system and the traditional costing system. The traditional system involves establishing cost items (such as salary cost, material cost, overhead and depreciation) based on cost items included in profit-and-loss statements. Calculation is dependent on whether a cost item could be directly charged to a patient: If a cost item could be directly charged to patients, the system then assesses only the

cost items that could be directly charged to the patient. Data on most of these items that use direct charges can be extracted from the claims data in the Japanese payment system. On the other hand, if a cost item could not be directly charged to patients, cost units are then established, according to direct and indirect departments. Direct departments (such as wards, radiology and specialized medical departments) are involved directly in the diagnosis and/or care of patients. Indirect departments (such as medical administration, accounting and medical records management) are not directly involved in diagnosis and/or care of patients. This traditional costing system is extremely time- and labor-intensive, and as such there is a tendency for costs from indirect departments, such as personnel costs in administrative staff that have little or no direct association with a patient, to be un-reflected in patient-level costs. The non-inclusion of entire sections of costs greatly reduces the accuracy of patient-level costing. In contrast, our new costing system includes all resources (and therefore all corresponding costs) used by each patient. The use of function tracing to produce patient-oriented costs (using both direct tracing and tracing by function drivers) was able to offset the shortfalls inherent in traditional methods of costing.

In summary, our new costing system was able to work in the complicated characteristics of health care costing, and improved the accuracy and the feasibility of patient-level costing.

Conclusions

Despite the difficulties in calculating patient-oriented costs, advances in the performance of

costing have been achieved by the new "function tracing" methodology. Patient-level costs are more accurate through more efficient processes than those calculated using traditional costing, and are therefore better suited for supporting decision-making at the hospital levels and also at the governmental policy levels. Our system of costing was also shown in practice to have improved efficiency over the traditional method, and we believe that this new methodology will be advantageous to hospital management, third-party payers and government policymakers.

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Figure 1. Calculation method of the new patient-oriented costing system using function tracing

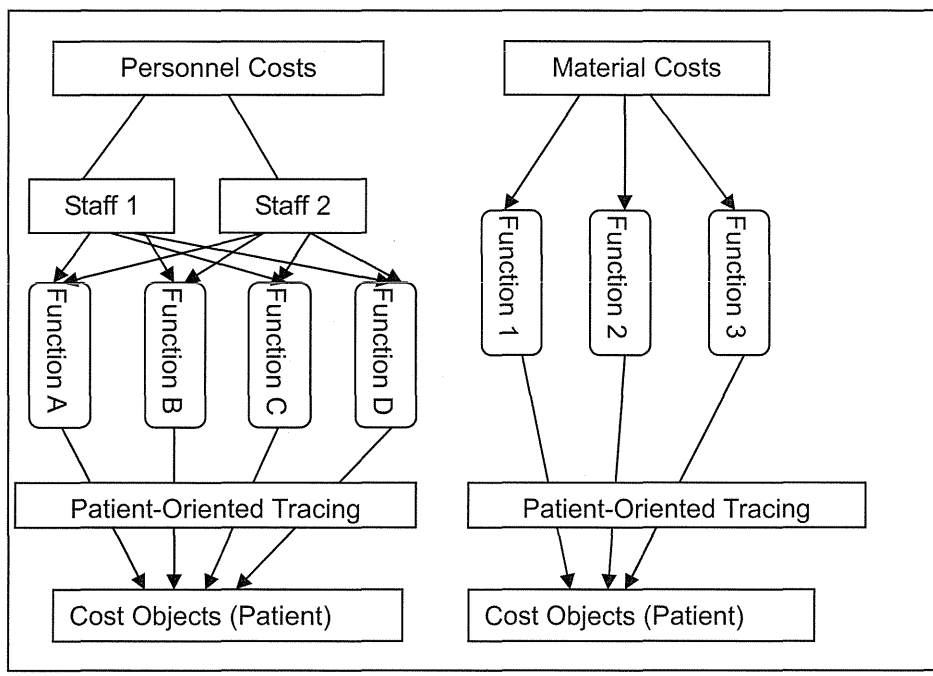


Figure 2. Multi-institutional comparisons of hospital costs and cost components in patients with angina

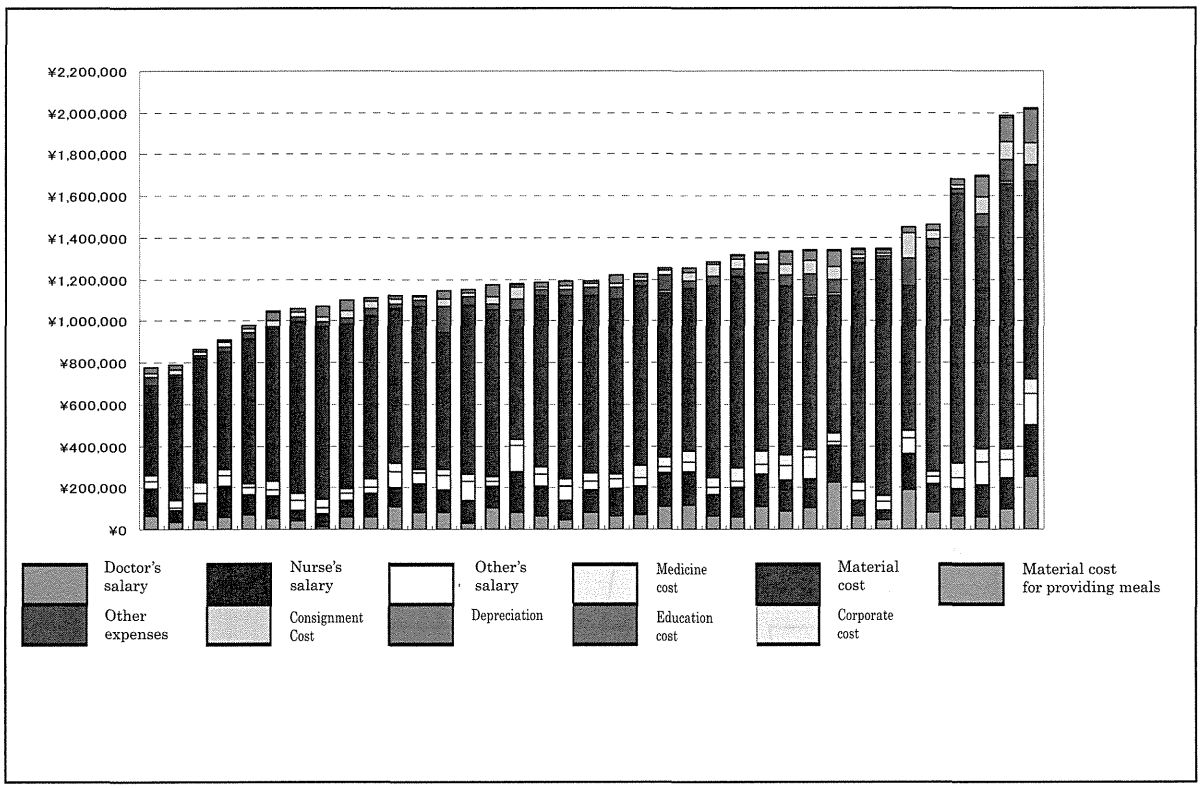


Figure 3. Model of patient-oriented costing using function tracing

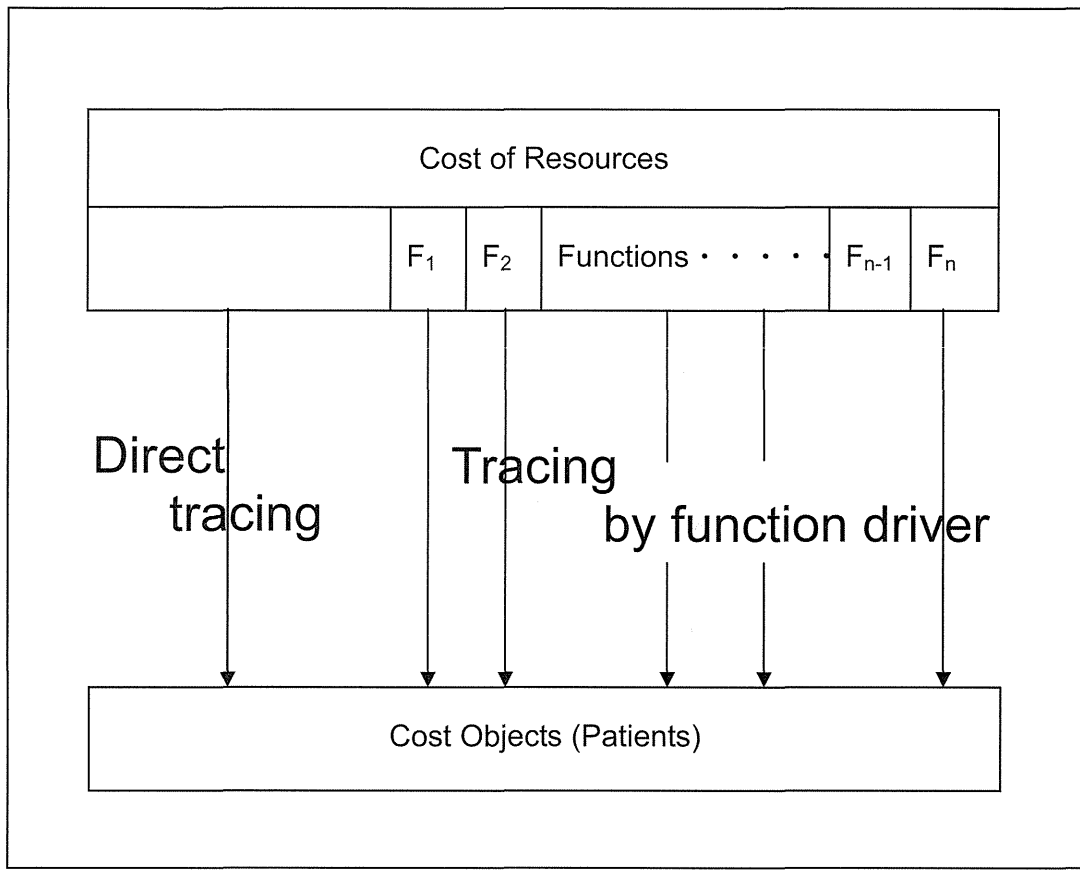


Figure 4. Mean daily health care costs and cost components of patients with pneumonia

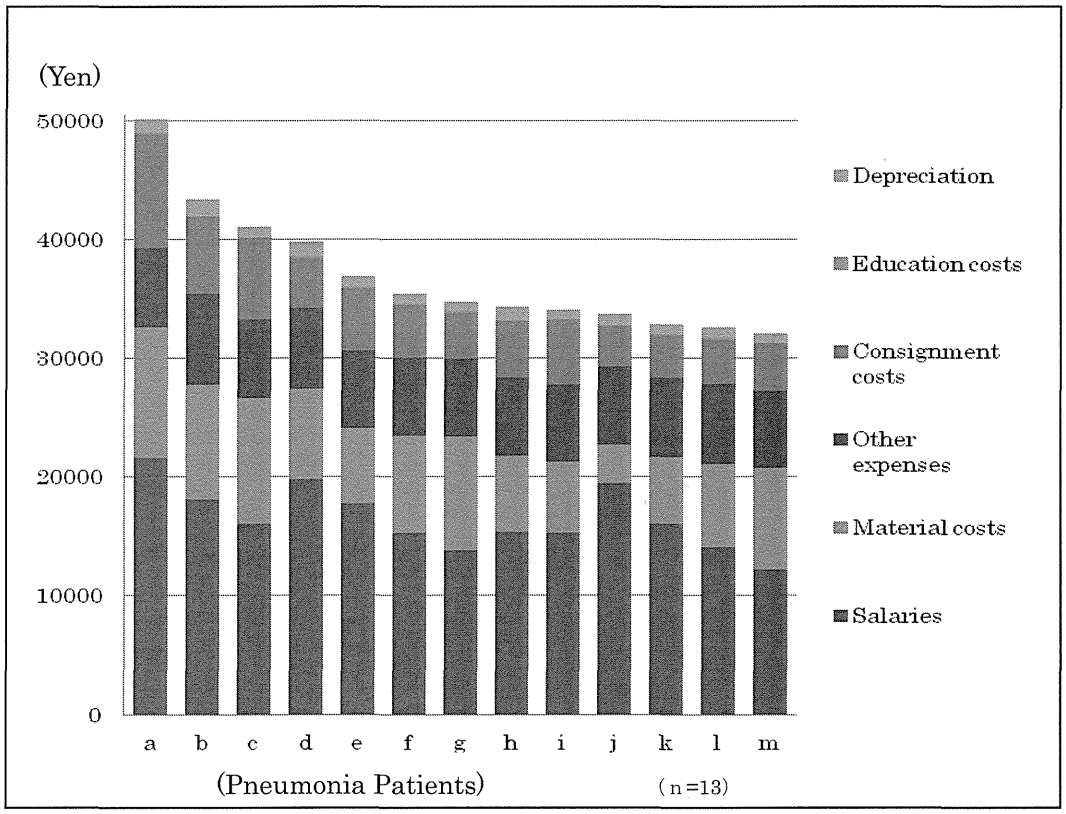


Figure 5. Mean daily hospital cost, income and profit of patients with pneumonia

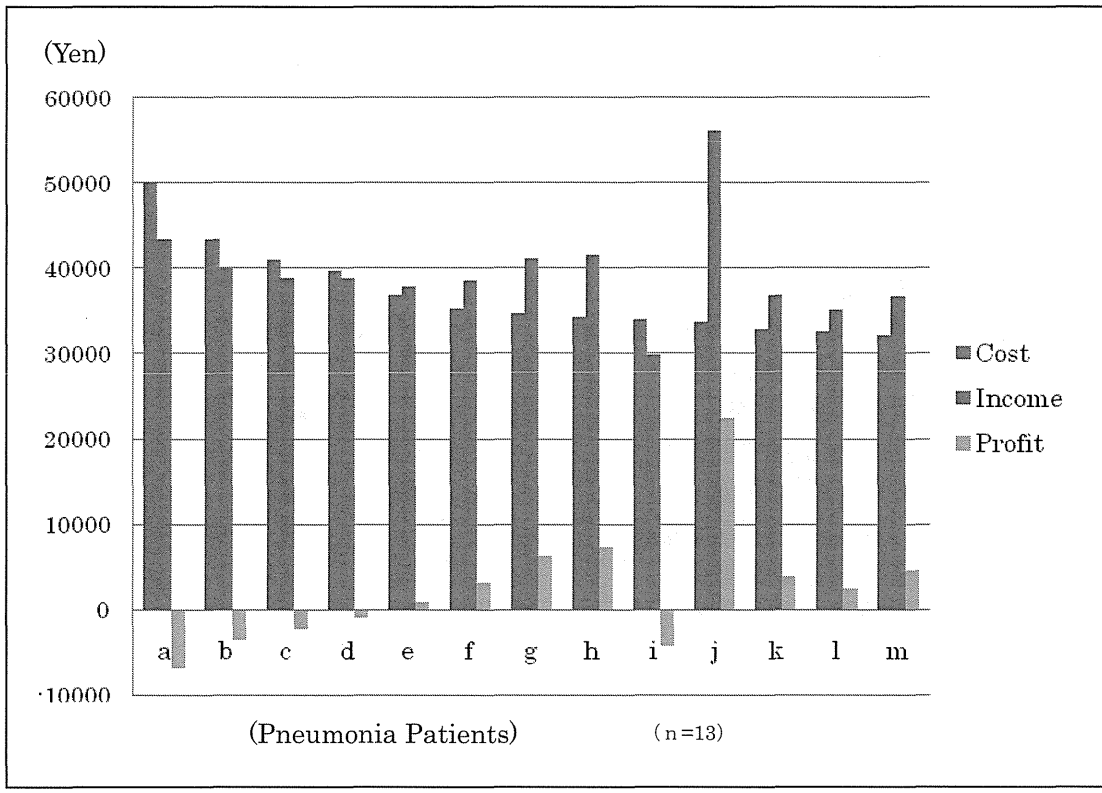


Figure 6. Mean hospital cost components by Major Diagnostic Category (MDC) in a hospital

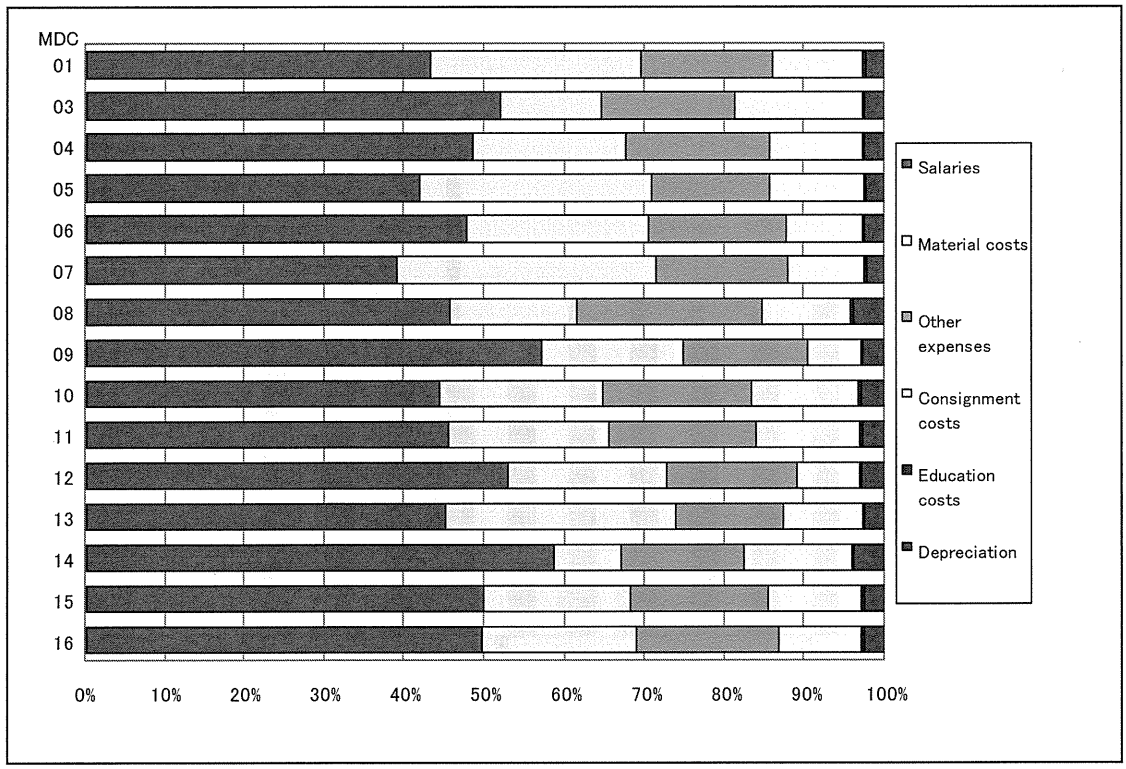
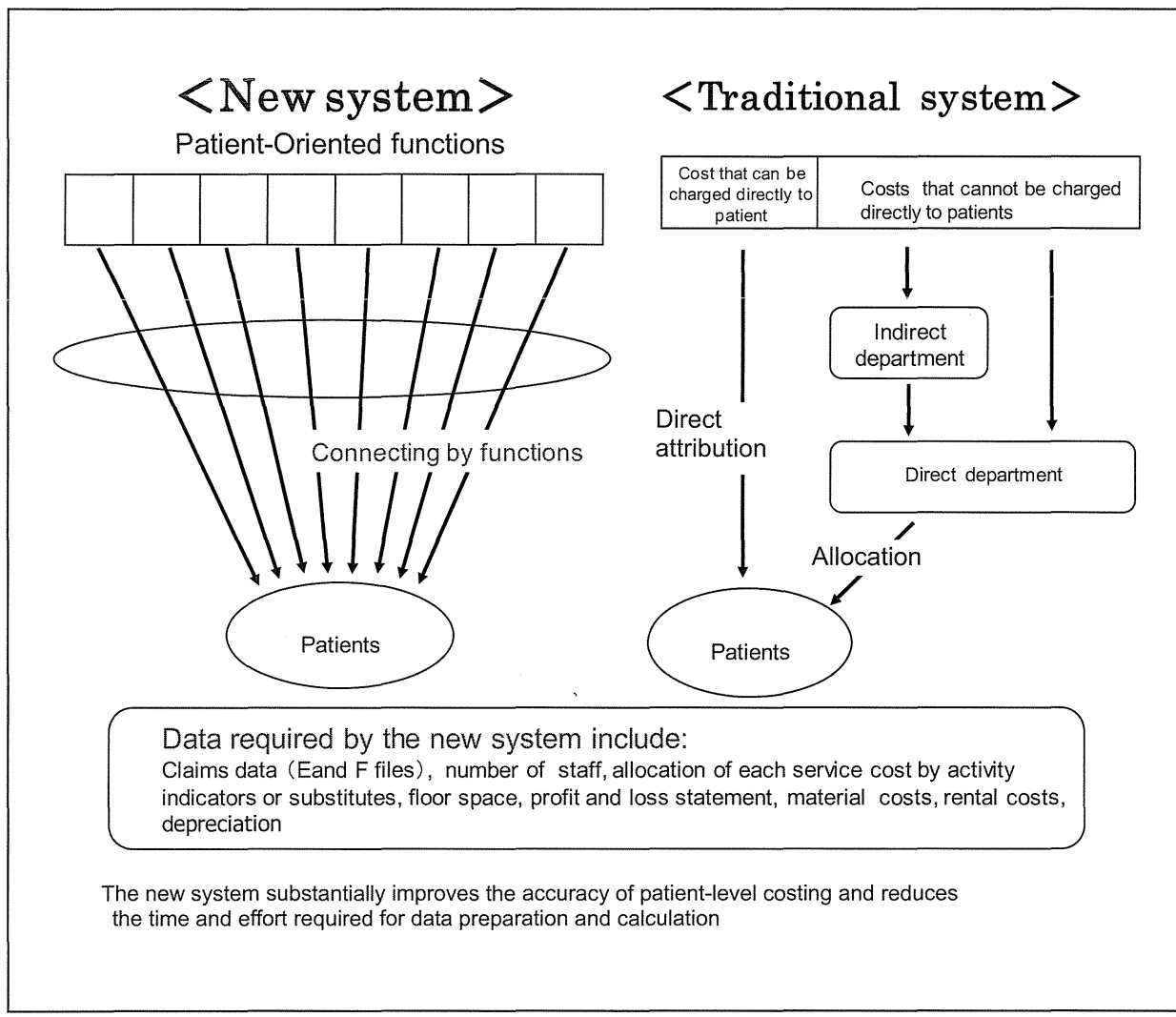


Figure 7. Differences between the new costing system and the traditional costing system



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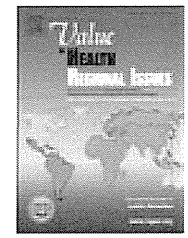

Cost-Effectiveness Analysis of Omalizumab for the Treatment of Severe Asthma in Japan and the Value of Responder Prediction Methods Based on a Multinational Trial

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ABSTRACT

Objectives: Omalizumab improves health outcomes for patients with severe asthma. The purpose of this study was to conduct a cost-utility analysis of omalizumab from a societal perspective by using the results from a randomized controlled trial in Japan, and explore the efficient use of omalizumab. **Methods:** We developed a Markov model to compare omalizumab add-on therapy with standard therapy. Patients transitioned between symptom-free, day-to-day, and exacerbation states. Our model had a lifetime horizon in which 5-year omalizumab add-on therapy was followed by standard therapy. Preference-based utilities were extracted from another study. We estimated the expected value of perfect information for patients' response to omalizumab. **Results:** In the base case, incremental cost-effectiveness ratio (ICER) for omalizumab add-on therapy was US $755,200 (95% credible interval [CI] $614,200–$1,298,500) per quality-adjusted life-year gained, compared with standard therapy alone. One-way sensitivity analyses indicated that the results were sensitive to asthma-related mortality, exacerbation risk, and omalizumab cost. The ICER for a responder subgroup was 22% lower than that in the base case. Individual and population expected value of perfect informations for the response were $4100 (95% CI $2500–$6000) and $28 million (95% CI $17 million–$42 million) per year, respectively. **Conclusions:** With a willingness-to-pay of $45,000 per quality-adjusted life-year, omalizumab was not cost-effective in Japan. Confining omalizumab therapy to previously predicted responders, however, may be a reasonable strategy to reduce the ICER, as the cost-effectiveness was observed to improve for these patients. Further studies should be conducted to explore responder prediction methods. Decreasing the price of omalizumab would improve cost-effectiveness.

Keywords: costs and benefits, decision making, economic evaluation, pharmacoeconomics, value of information.

Introduction

With an estimated 300 million patients worldwide, asthma is a common chronic disease that is recognized as a global public health problem [1]. Clinical features of asthma in most patients are well controlled with inhaled corticosteroids (ICS) via their anti-inflammatory effects, whereas persistent asthma in some patients is difficult to control with standard medications, including ICS, and is designated severe asthma [2]. Patients with severe asthma are obliged to decrease their health-related quality of life (HRQOL), visit emergency departments, and become hospitalized.

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to IgE and inhibits its interaction with the IgE receptor. Many clinical trials have shown that omalizumab reduces exacerbation risk and improves HRQOL related to asthma [3–6]. Omalizumab, however, is an expensive medication (US $1874 per 4 weeks on average). Several economic evaluation studies have been published [7–11]. Some of the findings from these studies have been unfavorable for omalizumab, whereas others have indicated the cost-effectiveness of omalizumab in patients with a history of severe exacerbations and hospitalization. The National Institute for Health and Clinical Excellence has recommended omalizumab as an add-on therapy with optimized standard therapy only in adults and adolescents with severe asthma and recurrent severe exacerbations [12].

Omalizumab is making a growing contribution to the treatment of severe asthma worldwide as an increasingly used therapeutic modality [5,6]. What is needed to increase the cost-effectiveness of omalizumab? One measure may be to develop prediction methods for patients' response to omalizumab ahead of omalizumab therapy. Omalizumab has been reported to provide different benefits for patients with severe asthma [3,4], although a prediction method for identifying responders has not been developed [5,6]. Predicting the response can contribute to minimizing unnecessary drug exposure and health care costs for nonresponders, who do not adequately respond to the therapy.

Previous studies and National Institute for Health and Clinical Excellence recommendations have been based on clinical data from large studies performed in many countries, excluding Asian countries. The first randomized controlled trial (RCT) that

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enrolled Asian patients with severe asthma was performed in Japan [13,14]. Patients with severe asthma constitute a major burden on the Japanese health care system due to their high requirements for inpatient care [1]. Japan's medical fees for health care services are relatively low among Organisation for Economic Co-operation and Development countries [15]. The price of omalizumab differs among different studies ($635 in our study, $489 [7], $522 [8], $562 [9], $568 [10], and $433 [11] per a 150-mg vial). These facts beg the question of whether omalizumab is cost-effective in the Japanese setting.

The aims of this study were to assess the cost-effectiveness of omalizumab in Japan by using clinical data from the RCT and cost data, and to explore the efficient use of omalizumab.

Methods

Our cost-utility analysis was performed from the societal perspective. The benefits of omalizumab, including effects on HRQOL, exacerbation risk, and mortality risk, were expressed as quality-adjusted life-years (QALYs) gained. The cost-effectiveness of omalizumab was expressed as an incremental cost-effectiveness ratio (ICER): omalizumab plus standard therapy (the omalizumab add-on group) versus placebo plus standard therapy (the standard therapy group). Standard therapy refers to treatments recommended prior to omalizumab therapy in the international clinical practice guidelines for the management of adult asthma [16]. Treatment was considered cost-effective if the ICER was below $45,000 (\5 million) per QALY gained [17]. Costs and benefits were discounted at 3% per annum. All costs were expressed as US dollars using the purchasing power parity rate for Japanese yen and European euro to US dollars in 2010 (\111 = $1, €0.805 = $1) from the Organisation for Economic Co-operation and Development National Accounts database. The models were developed by using TreeAge Pro 2009 Healthcare (TreeAge Software, Inc., Williamstown, MA).

Model Development

We developed a multistate transition model, or Markov model. The model structure was based on the following four states: symptom-free asthma, day-to-day asthma, asthma-related exacerbation, and death (Fig. 1). Symptom-free and day-to-day states were defined as no symptoms and relatively minor symptoms during the week, respectively. The exacerbation state was split into three mutually exclusive categories: mild exacerbation, severe exacerbation, and hospitalization. Mild exacerbation was defined as relatively major symptoms during the week. Severe exacerbation was defined as requiring treatment with systemic corticosteroids. We linked the hospitalization state with asthma-related death state. In previous economic evaluations of omalizumab [7–9], similar Markov models were used to evaluate the cost-effectiveness of omalizumab add-on therapy. We added the symptom-free state to the model used in previous studies so as to fit our model to end points that were assessed in the RCT in Japan.

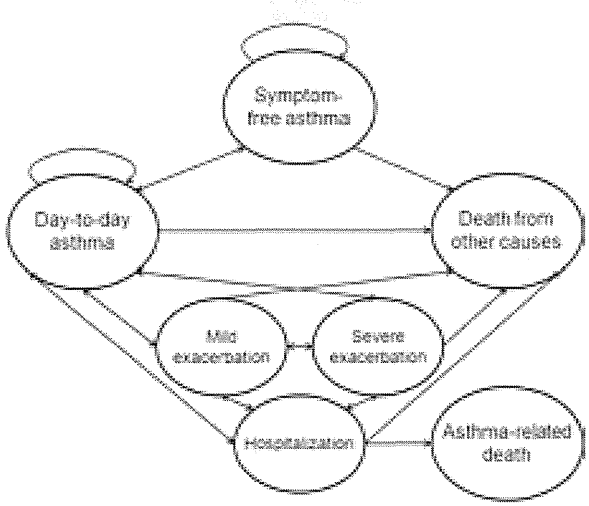

Fig. 1 – Markov model structure for economic evaluation of omalizumab.

The model cycle length was 1 week. The model had a lifetime horizon in which 5-year omalizumab add-on therapy was followed by standard therapy alone. The 5-year treatment duration was selected because of its use in previous studies [7–9], and represents a "compromise between the observed treatment duration in trials and the increased assumptions and uncertainty associated with the costs and outcomes of lifelong treatment" [9]. The study cohort matched the RCT population with an average age of 50 years and 50% men.

Clinical Input

We used clinical data from the intention-to-treat population of the RCT in Japan [13,14]. The RCT was a randomized, placebo-controlled, double-blinded, multicenter study. Omalizumab was evaluated for a 16-week treatment phase in 315 patients, aged 20 to 75 years, with moderate-to-severe persistent asthma despite high-dose ICS and other controller medications. The RCT assessed the number of symptom-free weeks, mild exacerbation weeks, severe exacerbation weeks, and hospitalizations for each patient. The RCT measured asthma symptom scores, which were a sum of exacerbation (range 3–9), wheezing (1), and cough (range 0.5–1) scores, with a score of 0 denoting no symptoms. Symptom-free weeks were defined as a total symptom score of 0 during the week. Mild exacerbation and severe exacerbation were defined as experiencing major symptoms to some degree and requiring systemic corticosteroids, respectively.

The number of exacerbation weeks experienced by patients was published for each treatment group. Rates were calculated as per person-week. Rate ratios were calculated as the ratio of the omalizumab add-on group compared with the standard therapy group. Transition probabilities were obtained with the following formula: 1 – exp(–rate).

The incidence of serious adverse effects, such as anaphylaxis, was rare and similar in patients treated with omalizumab and placebo [13,14]. The same was reported for a large multicountry study [3]. Therefore, we did not incorporate any adverse effect costs or utility decrements for either treatment group into our model.

Response to Omalizumab

Patients with severe asthma derive different benefits from omalizumab [3,4]. It is difficult to predict the extent of benefits derived by various patients based on pretreatment characteristics [5,6]. Responders are identified by physicians' global evaluation of treatment effectiveness after 16-week omalizumab therapy [5,6]. Omalizumab add-on therapy is discontinued at 16 weeks in nonresponders [5,6,12]. In our model, nonresponders reverted to standard therapy alone after the termination of omalizumab add-on therapy at 16 weeks. Responders were not identified in the RCT in Japan. We incorporated a response rate of 60.5% into our model [3,4].

Primary Utility Estimate

Because of the lack of detailed HRQOL measures in the RCT, we derived preference-based utility values from one previous study

[18], which reported utility values of asthma control levels (good, mildly reduced, moderately reduced, and poor control) using the EuroQol five-dimensional questionnaire index. Although the asthma control levels described by this previous study [18] did not perfectly fit our model, we regarded symptom-free, day-to-day, and mild exacerbation states as "good control," "mildly reduced control," and "moderately reduced control," respectively, and severe exacerbation and hospitalization states as "poor control" for the purpose of utility estimates.

Alternative Utility Estimate

To examine the impact of utility estimates on the results, we conducted additional analyses by using another set of utility values reported by another previous study [19], which examined utilities associated with asthma exacerbations by using a visual analogue scale. We regarded day-to-day and mild exacerbation states as "current asthma state" and "mild exacerbation," respectively, and severe exacerbation and hospitalization states as "severe exacerbation." This previous study did not examine values for the symptom-free state. We made an arbitrary and extreme assumption that the utility value for patients in the symptom-free state was 1. This assumption created a bias in favor of omalizumab because patients in the omalizumab add-on group were more likely to be in the symptom-free state than in the standard therapy group.

Mortality

No fatalities were recorded in the RCT [13,14]. Our model, however, included asthma-related death and death from other causes because the Asthma Policy Model included both types of death [20]. We calculated asthma-related mortality risk among hospitalized asthmatic patients by using Japan's official databases [21,22]. Age-specific risk of death from other causes was based on Japan's vital statistics [22].

Cost Input

Direct health care costs of omalizumab, standard therapy, and health care resource use for exacerbation and direct non–health care costs of transportation were included in our model. These unit costs were obtained from Japan's official database [23] and our department's Quality Indicator/Improvement Project, which collects clinical and claims data from more than 200 hospitals in Japan. Productivity loss cost of survivors and deceased patients was not included in the model.

Omalizumab is administered by subcutaneous injection. An approximate dose is defined according to each patient's body weight and serum IgE level. Patients receive 75 mg, 150 mg, 225 mg, 300 mg, or 375 mg of omalizumab every 2 or 4 weeks. Mean dose and mean number of 150-mg vials per patient per 4 weeks were 398 mg and 2.95 vials, respectively, based on the dose distributions observed in the RCT [14].

In Japan, omalizumab is wasteful for some patients in terms of product content. For example, a patient who is administered 225 mg of omalizumab every 2 weeks requires four 150-mg vials per 4 weeks. This is because an omalizumab vial is for single use only; any remaining unused content is discarded. If 75-mg vials were available, the patient in the above example would require six 75-mg vials per 4 weeks. In the sensitivity analysis, we assumed that the 75-mg vial would be developed and approved in Japan and that the price of a 75-mg vial would be half the price of a 150-mg vial.

To obtain standard therapy costs, we assumed that standard therapy consisted of high-dose ICS, long-acting beta agonists, theophylline, and leukotriene antagonists, which are all recommended prior to omalizumab therapy in the international clinical practice guidelines [16]. As a combination therapy of high-dose ICS and long-acting beta agonist, we considered the salmeterol/fluticasone combination (500 μg, one puff twice daily) for the base-case analysis and the budesonide/formoterol combination (160 μg, four puffs twice daily) for the sensitivity analysis. The omalizumab add-on group as well as the standard therapy group incurred standard therapy costs. We did not consider generic drugs.

We assumed that a patient in a severe exacerbation state made one visit to the emergency department and that emergency department visits and hospitalizations required transportation costs.

Sensitivity Analysis

We performed probabilistic sensitivity analysis with 5000 Monte Carlo simulations to obtain 95% credible intervals (CIs) for outputs of the model. We also performed one-way sensitivity analyses to estimate the impact of the range (95% confidence interval) of rate ratios (but not going above or below 1), utility values, omalizumab cost, and our assumptions on the results. To estimate the impact of utility values, we ran utilities over an arbitrary range from 10% above to 10% below each value (but not going above 1) by using the primary utility set. We also evaluated the following scenarios: different asthma-related mortality, different standard therapy cost, different unit cost of emergency department visit, different unit cost of hospitalization, different transportation cost, and different discount rate. We conducted a threshold analysis to provide the break-even price of omalizumab for the base case. In addition, we performed a subgroup analysis in which the target population was assumed to suffer from particularly severe asthma, with exacerbations rate double that of the base case and a symptom-free rate half that of the base case.

The Value of Information Analysis

The expected value of perfect information (EVPI) is the price that the health care system would be willing to pay to conduct further research and gain access to perfect information because perfect information can eliminate the possibility of making a wrong decision based on existing (prior) information [24]. Administering omalizumab to nonselective patients leads to the treatment of nonresponders, which results in wasteful health care expenditure. Prediction methods for the identification of responders ahead of omalizumab treatment would help physicians avoid the unnecessary treatment of nonresponders.

The ICER of omalizumab add-on therapy in the responder subgroup relative to the standard therapy group was calculated by subgroup analysis. The responder subgroup was entirely composed of responders receiving 5-year omalizumab therapy. Clinical outcomes for the responders were further improved when compared with the total number of patients treated with omalizumab [3,4]. The clinical parameters of responders from the large multicountry study were incorporated into our model [5,25,26].

We estimated the individual EVPI for the omalizumab response from the difference in net monetary benefits between the omalizumab add-on group (i.e., the total number of patients treated with omalizumab) and the responder subgroup. We then calculated the population EVPI per year for the total number of expected patients in Japan by multiplying the individual EVPI (minus screening costs for each patient) by the incidence of eligible patients, which was estimated from the incidence of adult asthma (3.6/1000 and 4.6/1000 person-year in men and women, respectively) [27] and the proportion of severe asthma (1.6%) [28]. We assumed that the screening test for each patient cost $180, which is similar to the cost of gene mutation testing in Japan.

Table 1 – Clinical inputs and cost inputs in our economic model.

	Standard therapy group	Omalizumab add-on group*	Responder subgroup†	Source
Rate per person-week and risk ratio				
Symptom-free rate	0.16	RR 1.68 (95% CI 1.48–1.91)	RR 2.03 (95% CI 1.49–2.81)	[13,14,25]
Mild exacerbation rate	0.067	RR 0.55 (95% CI 0.43–0.71)	RR 0.40 (95% CI 0.29–0.55)	[5,13,14,26]
Severe exacerbation rate	0.0069	RR 0.36 (95% CI 0.14–0.91)	RR 0.24 (95% CI 0.12–0.50)	[5,13,14,26]
Hospitalization rate	0.0015	RR 0.27 (95% CI 0.03–2.43)	RR 0.24 (95% CI 0.13–0.42)	[5,13,14,26]
Utility for initial and reproducibility analyses‡				
Symptom-free asthma		0.93 (1)		[18] and assumption
Day-to-day asthma		0.76 (0.81)		[18,19]
Mild exacerbation		0.65 (0.62)		[18,19]
Severe exacerbation		0.52 (0.26)		[18,19]
Hospitalization		0.52 (0.26)		[18,19]
Mortality				
Risk of death from asthma given a hospitalization		0.0155		[21,22]
Proportion of responders		60.5%	100%	[3,4]
Direct cost ($)				
Standard therapy cost per 4 wk for base case		147		Model case
Standard therapy cost per 4 wk for sensitivity analysis		274		Model case
Omalizumab cost per 4 wk, using 150-mg vial ($635/vial)		1874		[13,14]
Omalizumab cost per 4 wk, using 75-mg vial ($318/vial)§		1686		[13,14]
Median unit cost of emergency department visit (interquartile range)		79 (55–158)		QIP‖
Mean unit cost of hospitalization		2203		[23]
Non–health care cost ($)				
Transportation cost per visit or hospitalization		20 (10–40)		Assumption

CI, confidence interval; RR, rate ratio relative to standard therapy group.

* Omalizumab add-on group indicates the total number of patients treated with omalizumab plus standard therapy.

† Responder subgroup indicates a subgroup of patients who derive great benefits from omalizumab plus standard therapy.

‡ Utility values inside and outside of parentheses are used as the primary utility set and the alternative utility set, respectively.

§ Omalizumab 75-mg vials are unavailable now in Japan and based on our assumption.

‖ QIP indicates our department's Quality Indicator/Improvement Project, which collects clinical and claims data from more than 200 hospitals in Japan.