Mini Review

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Evidence-based medicine for gallstone disease screening: an experience at cheng-hsin general hospital, Taipei, Taiwan

Abstract

Epidemiologic and clinical studies have shown that gallstone disease is a common gastrointestinal disease; more than 14% of adults are affected by this disorder. From the preventive medicine perspective, the most crucial topic for preventing gallstone disease is how to achieve early detection and early treatment by using effective screening tools. To understand the morbidity rate of gallstone disease and to prevent its occurrence requires considering the progression of the disease. Early prevention of gallstone disease necessitates understanding the relevant risk factors of gallstone disease occurrence and its transitional influence. This paper discusses the epidemiologic and economic evaluation of gallstone disease based on a hospital-based screening experience in Taipei, Taiwan. This screening experience will hopefully provide additional information for establishing screening strategies and health management programs for gallstone disease.

Keywords: gallstone disease, screening, evidence-based medicine

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Abbreviations: GSD, gallstone disease; OC, open cholecystectomy; LC, laparoscopic cholecystectomy; WTP, willingness-to-pay; NTD, new Taiwan dollars

Introduction

Gallstone disease (GSD) has been considered a major public health problem in developed countries.[1] Its prevalence ranges from 10% to 15% in adults and medical expenses for GSD treatment have exceeded 6 billion USD in the United States.[2,3] Depending on the clinical manifestation and expectant management, cholecystectomy still represents the standard therapeutic approach for patients with symptomatic GSD.[4] In Taiwan, the prevalence of open cholecystectomy (OC) gradually decreased from 18.19 to 13.21 per 100 000 patients, whereas laparoscopic cholecystectomy (LC) increased from 25.44 to 48.35 per 100 000 patients. The total clinical treatment costs for OC and LC are estimated to be 2729 and 1588 USD, respectively.[5] The choice of ultrasound scanning in GSD evaluation is ideal because it is cheap, noninvasive, safe, and repeatable without known adverse effects to patients in clinical scenarios.[6] From the preventive medicine perspective, early detection of this gastrointestinal disorder by routine screening followed by appropriate treatment may reduce cholecystectomies. This study explored the experience of a regular screening program for GSD at Cheng-Hsin General Hospital, a teaching hospital in Taipei, Taiwan.

Screening methods for gallstone disease at cheng-hsin general hospital

Data source and collection

Figure 1 shows the procedures for GSD screening. Between January 1, 2002 and December 31, 2007, a total of 2386 healthy adults (1235 men and 1151 women) were voluntarily admitted to Cheng-Hsin General Hospital, a fully certified regional and teaching hospital with 1030 beds in Northern Taiwan, for an annual physical check-up. All procedures were performed according to the guidelines of the Cheng-Hsin General Hospital ethics committee and adhered to the tenets of the Declaration of Helsinki. The data from all participants remained anonymous. Access to personal medical records was approved by the institutional review board at Cheng-Hsin General Hospital in Taipei, Taiwan.

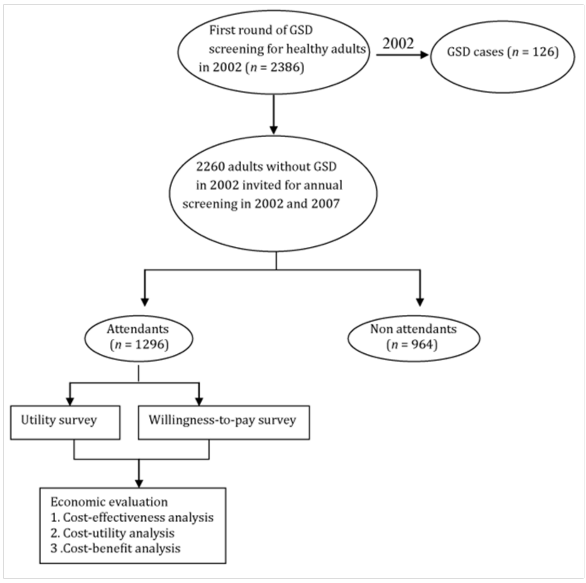

Figure 1 Screening procedure for gallstone disease among healthy adults at cheng-hsin general hospital during 2002–2007.

Diagnosis of gallstone disease

In this screening program, a panel of specialists used real-time ultrasound sonography (TOSHIBA Nemio SSA-550A, Japan) to examine the abdominal region after fasting for at least 8 hours based on the presence of movable hyperechoic material with acoustic shadow. Cases of GSD were excluded as gallbladder polyps when classified with no GSD or with single stone, multiple stones, or cholecystectomy.

The kappa statistic was applied to assess the agreement of interobserver reliability among study specialists before establishing a consistent diagnosis of GSD. A pilot study was established using 100 randomly selected participants in addition to the healthy study participants. For estimating interobserver reliability, the kappa value for consistent diagnosis of GSD between two specialists was 0.79 (95% CI: 0.61-0.95).

Utility and willingness-to-pay evaluation

Patients from 120 outpatient clinic sites aged 30 years or above (30 participants with no GSD, 30 participants with a single stone, 30 participants with multiple stones, and 30 participants with cholecystectomy) were interviewed to evaluate the utility and willingness-to-pay (WTP) for GSD screening. Each eligible participant was first asked whether he or she would be willing to answer utility and WTP-related survey questions, and confirmed their willingness to participate by signing an informed consent. People were excluded from the analysis if they were unwilling to answer the utility and WTP questions related to GSD. The utility evaluation from the time trade-off method was based on the standard procedure.[7,8] The entire scenario was described as follows: "Suppose a situation in which you could only live 10 years under your current health status. An opportunity exists that could return your health status to full health. This opportunity could increase your quality of life, but reduce your survival time. What is the maximum number of years you would be willing to give up if you could receive this opportunity and have full health for the remainder of your life?" The utility value was then calculated by dividing the number of years a person was willing to trade for improved quality of life by the estimated number of years of remaining life, and subtracting this number from 1.0, that is, utility value=1.0 (time traded/time of remaining life).[7,8] For example, the utility value would be calculated as 0.9 (1.0 (1/10)) if a person expected to live 10 additional years and would trade one year in return for perfect health status.

According to welfare economic theory, the benefit to an individual of a service or intervention is defined as that individual's maximum WTP value for the service or intervention based on welfare economic.[9] The payment vehicle not only refers to the means of payment by a patient, but also is assumed as total cost of both copayments for health insurance scheme and out-of-pocket money which is not covered by health insurance benefit.[10] In this study, WTP was estimated according to the following question: "What is the highest price (New Taiwan Dollars) you would be willing to pay for routine screening for GSD that reduces the risk of receiving cholecystectomy?" WTP value for GSD screening was produced through discrete choice. Study participants were presented a single price for a routine GSD screening program that would yield a specified health change, and could either accept or reject the price. Varying the price across numerous subsamples produced the mean WTP.[9] All information on WTP measurements was collected by one well-trained interviewer in order to maintain consistent interview quality. The participants were also encouraged to provide honest answers based on their income and financial status.

Natural progression model of gallstone disease

In the GSD screening at Cheng-Hsin General Hospital, the four-state Markov chain model for the natural course of GSD following the proliferative phase pathway was mapped as follows:

$$\underset{(State\ 1)}{No\ GSD} \xrightarrow{\lambda_{12}} \underset{(State\ 2)}{Single\ stone} \xrightarrow{\lambda_{23}} \underset{(State\ 3)}{Multiple\ stones} \xrightarrow{\lambda_{34}} \underset{(State\ 4)}{Cholecystectomy}$$

To quantify the progression rates, let λ_{12} represent the instantaneous progression rate from State 1 to State 2, λ_{23} from State 2 to State 3, and λ_{34} from State 3 to State 4. Based on the Markov property, the inverse of λ_{23} and λ_{34} represents the mean duration of states with a single stone and multiple stones, respectively. Therefore, the mean duration in each state was estimated by modeling the age at diagnosis of the state for each person at first assessment with a continuous time.[11]

Economic evaluation of gallstone disease screening

The economic evaluation tool in this screening program was used to assess GSD screening based on the TreeAge software (DATA 3.5, Tree-Age, Inc., Williamstown MA) for medical-decision analyses. This software uses the influence diagram approach and tree structure. By using the Markov Decision Model, a decision analysis was constructed to compare various screening regimes for GSD with the no-screening group. The statistical assumption of the no-screening group was that except for GSD screening, patients continued to receive routine medical care until cholecystectomy. According to stochastic process theory, the Markov chain model was determined by both the initial disease state and the transition matrix. This model begins with the decision of the participant to undergo screening or no screening, and the overall expected value is based on the expected values of the end nodes rather than all nodes. For each situation, the expected probability based on participants' aggregate experiences was calculated using data accumulated for each stage during the 10-year follow up.

In this hospital-based screening, both the direct and indirect costs were analyzed. Direct costs included the cost of routine GSD screening, cost of regular clinical fees, and further treatment costs. For indirect costs, we included only the loss of patient productivity because of time off work for treatment. Because the participants were not accompanied by an attendant every time, attendant costs were not considered. The average time off work for treatment was estimated by the specialists. All considered costs were expressed in New Taiwan dollars (NTD). We conducted a cost-effectiveness analysis to compare the cost per life-year gained by the screened patients relative to the nonscreened group. To adjust for quality of life, a series of utility scores was assigned based on a cost-utility analysis. In addition, by using the human-capital approach, the net cost (savings) for various GSD screening regimes was calculated after considering direct and indirect costs. Benefit-cost ratios were calculated as reduced cholecystectomy costs divided by the cost of the screening programs. The net present value was calculated based on the total benefit minus the screening cost of GSD by using the WTP approach. All costs and benefits to the present value were annually discounted by 5% to account for time preference, and the present value received the benefits earlier and incurred the costs later.

Results of the screening program for gallstone disease at cheng-hsin general hospital

Basic epidemiology of gallstone disease screening

Among the 2386 patients, 126 were diagnosed with GSD. The overall prevalence of GSD was estimated to be 5.3%; 1.7% had a single stone, 2.3% had multiple stones, and 1.3% had a cholecystectomy. Women (3.0%) exhibited a significantly higher prevalence of multiple stones than did men (1.7%) (P=0.04). Participants aged 50 years and older (96/918=10.5%) had a 5-fold risk for prevalent GSD compared with those aged 50 years and younger (30/1468 = 2.0%).[12]

All patients who participated in at least two GSD screenings were analyzed for incident estimation; however, 964 (42.7%) failed to complete the series of assessments. The annual incidence of GSD was 0.632% (95% CI: 0.191%–2.009%), indicating a clear age-trend (P=0.03) where values monotonically increase. The annual incidence increased from 0.214% (95% CI: 0.062%–1.719%) at ages < 40 years to 0.470% (95% CI: 0.112%–2.103) at ages 40–49 years, 0.585% (95% CI: 0.236%–1.983%) at ages 50–59 years, and 1.394% (95% CI: 0.410–2.477%) at ages greater than 60 years. We observed no consistent patterns in age groups. Women demonstrated a slightly higher annual incidence (0.741% versus 0.496%, P=0.40) compared with men, but the sex difference was nonsignificant. Subsequent to adjustment for confounding factors, age, elevated body mass index, elevated fasting plasma glucose, and nonalcoholic fatty liver disease were the predictors significantly related to GSD development.[13]

Estimations of the multistate disease model of gallstone disease

Based on data from the follow-up cohort and transitions between states of GSD, types of transition, transition history, number of transitions, and transition probabilities, annual progression rates from single stones to multiple stones and from multiple stones to cholecystectomy were estimated at 0.114 (95% CI: 0.015-0.173) and 0.148 (95% CI: 0.101-0.242), respectively. The corresponding mean duration in single stone and multiple stone states were 8.77 (95% CI: 5.78-66.67) and 6.76 (95% CI: 4.13-9.90) years, respectively. The application of parameters to the annual transition probabilities from single stone to multiple stones and from multiple stones to cholecystectomy were 10.00% and 13.76%, respectively.

An annual screening regimen reduced cholecystectomy by 82.9% (95% CI: 75.7%-90.4%) compared with the control group. Comparatively, biennial screening reduced cholecystectomies by 71.6% (95% CI: 57.0%-88.8%), whereas a 3-year screening regimen reduced cholecystectomy by 64.8% (95% CI: 46.1%-81.5%). The corresponding figures for 4- and 5-year screening intervals were 49.6% (95% CI: 23.9%-75.3%) and 32.1% (95% CI: -2.8%-66.7%), respectively.[11]

Economic evaluation of screening for gallstone disease

In the utility survey more than 40% of the participants answered that their utility value was 1.0 and implied that they had perfect health status. Approximately 8% of participants answered that their utility value was below 0.7 and 10% of participants were unable to provide the number of years that they would trade for full health when presented with the utility question. The mean utility value was estimated to be 0.89 ± 0.11 (95% CI: 0.87-0.91) and revealed that these participants were willing to trade approximately 11% (95% CI: 9%-13%) of their remaining life to be perpetually free of GSD.[8] In addition, the average WTP value of those who answered "Yes" was 403.9 ± 238.0 NTD (13.4 ± 7.9 USD) (30.2 NTD=1 USD). Participants with severe stage GSD exhibited higher WTP values for screening than did those with mild stage GSD [No GSD (248.4 ± 178.9 NTD) vs single stone (335.3 ± 208.1 NTD) vs multiple stones (382.2 ± 221.8 NTD) vs cholecystectomy (470.5 ± 192.8 NTD)].

The cost per life-year gained (average cost-effectiveness ratio) for annual screening, biennial screening, 3-year screening, 4-year screening, 5-year screening, and no-screening was 39 076, 58 059, 72 168, 104 488, 126 941, and 197 473 NTD, respectively (P<0.05). The cost per quality-adjusted life-year gained by annual screening, biennial screening, 3-year screening, 4-year screening, and 5-year screening was 40 725, 64 868, 84 532, 110 962, and 142 053 NTD; and for the control group, 202 979 NTD (P<0.05). The threshold values indicated that the ultrasound sonography screening programs were highly sensitive to screening costs in a plausible range. In addition from the societal and health care payer's perspective, the various screening programs for GSD can save between 19.61 and 63.41 NTD, and between 2.89 and 4.71 NTD, respectively, in discounted costs for each dollar incurred in different screening years in the benefit-cost ratio. The average estimated WTP to translate into benefit yielded NTD from 807.8 to 4039 benefits per case because of GSD screening in different screening years during the 10-year follow up. The net present value of the GSD screening was from -133 736 to -217 689.2 NTD in different screening years.[14]

Discussion

Clinical implications of gallstone disease screening

The natural course of GSD is typically benign; however, its complications contribute substantially to healthcare costs and may even be life threatening.[15] A crucial benefit of early detection for GSD is that ultrasonography can detect asymptomatic cases, enabling appropriate treatment and prevention of serious influences such as acute gallstone pancreatitis or gallbladder cancer.[16,17] Few studies have explored the incidence of GSD and its possible etiology among the general population in Taiwan. The incidence of GSD varies among test populations and differs among studies explored in disparate countries.[1,13] Morbidity differed slightly—10 years apart—in two Italian studies, GREPCO and MICOL.[1,18] This may imply that the dietary habits of Taiwanese people have already been westernized.

The natural progression of the disease and screening recommendations for GSD must be understood because even advanced disease can occur in an asymptomatic phase. Regarding screening policy, the optimal screening interval is determined by the natural progression of the disease.[11] Most clinicians agree that the majority of asymptomatic patients should be managed conservatively; however, prophylactic cholecystectomy is indicated in defined subgroups at increased risk for developing GSD-related symptoms and complications.[19] The estimates of transition parameters in this study can be applied to evaluate the effectiveness of early detection of GSD or as clinical control for the general population. The progressive disease model of GSD suggests that estimates of mean sojourn times spent in the state of no-GSD, single stone, multiple stones, and cholecystectomy are 18.18 years, 8.77 years, and 6.76 years, respectively. Assuming no direct transition from the single stone stage to cholecystectomy, the average time for developing from no-GSD to cholecystectomy is approximately 33.7 years for the screened population.

GSD is matched with the Wilson criteria for screening because it is a major public health problem; the natural course of the disease should be explored; it comprises a recognizable latent or early symptomatic phase; a screening test is easy to perform and interpret and has acceptable, accurate, reliable and excellent sensitivity and specificity; it is an acceptable treatment method recognized for the disease; treatment is more effective if begun early; it includes a health policy on who should be treated; diagnosis and treatment are cost-effective and case-findings should be a continual process.[14] Economic evaluations have been criticized by medical decision makers for ignoring budget effects, for which decision makers are desperately concerned about. Payers might encounter financial difficulty if they adopt too many cost-effective and affordable interventions that rely on the overall volume of patients; this is therefore a primary concern.[4,14] Our results showed that an annual screening regimen can offer greater cost-effectiveness than any longer screening intervals can. Considering both cost and efficacy, suitable prevention programs aimed at GSD screening result in both a substantial federal budgetary reduction and highly cost-effective medical care.

Perceived limitations

One of major limitations to this study was the potential self-selection bias caused by the hospital-based study design and those aged 60 or over were only 18% of the sample and yet developed 48% of the GSD. The sample may not be representative of the general population. Second we assumed that all new GSD cases occurred during screening year. However, additional GSD cases could occur at any time during the screening period, the incidence of GSD could be underestimated. Third, we did estimate the incidence of GSD formation, but rather investigated the incidence of newly screened GSD, focusing only on clinically relevant GSD. Fifthly, we did not evaluate the post cholecystectomy syndrome, which not only can represent either the continuation of symptoms thought to be caused by the gallbladder or the development of new symptoms normally attributed to the gallbladder, but also includes the development of symptoms caused by removal of the gallbladder.[20] Should asymptomatic gallbladder stones be treated with cholecystectomy? This has important clinical implications not at least from a cost-benefit aspect. Post cholecystectomy syndrome may cause suffering and is costly in health care systems.

Conclusion

In conclusion, from the screening experience for GSD of Cheng-Hsin General Hospital, in addition to indicating a series of demographic and biochemical markers related to GSD, this hospital-based screening program also demonstrated the screening efficacy and optimal screening interval for early detection of GSD. The average time for the development of gallstone disease from nonexistence to cholecystectomy was approximately 33.7 years and annual screening interval of gallstone disease should be recommended. Further organized evaluation of quality of care programs should consider costs and benefits carefully before setting universal screening standards for GSD.

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Author Contributions

Zi-Hao Zhao and Tao-Hsin Tung drafted the manuscript. Chinh--Chinh Peng and Wu-Hsiung Chien coordinated the drafting of the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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