Table 5 Frequency of adverse events

Adverse events that occurred in the double-blind period	Lansoprazole ($n = 226$)	Gefarnate ($n = 234$)	P value
All adverse events	166 (73.5)	168 (71.8)	0.70
Causal relationship to drug not deniable	26 (11.5)	25 (10.7)	0.78
Leading to discontinuations	21 (9.3)	24 (10.3)	0.73
Serious adverse events	27 (11.9)	26 (11.1)	0.78
Causal relationship to drug not deniable	0 (0.0)	1 (0.4)	0.33
Deaths	0 (0.0)	0 (0.0)	–
Adverse events reported in at least 3% of the total in each group			
Nasopharyngitis	54 (23.9)	55 (23.5)	0.93
Constipation	14 (6.2)	8 (3.4)	0.17
Fall	13 (5.8)	9 (3.8)	0.34
Diarrhea	19 (8.4)	2 (0.9)	<0.001
Reflux esophagitis	3 (1.3)	16 (6.8)	0.01
Back pain	10 (4.4)	5 (2.1)	0.17
Elevated blood creatine phosphokinase levels	7 (3.1)	8 (3.4)	0.85
Eczema	5 (2.2)	7 (3.0)	0.61
Hypertension	7 (3.1)	3 (1.3)	0.19

Adverse events reported in patients who received lansoprazole throughout the double-blind and open-label study	Lansoprazole ($n = 339$)
All adverse events	279 (82.3)
Causal relationship to drug not deniable	55 (16.2)
Leading to discontinuations	39 (11.5)
Serious adverse events	51 (15.0)
Causal relationship to drug not deniable	1 (0.3)
Deaths	2 (0.6)
Adverse events reported in at least 3% of the total in each group	
Nasopharyngitis	113 (33.3)
Diarrhea	32 (9.4)
Constipation	23 (6.8)
Fall	19 (5.6)
Hypertension	17 (5.0)
Elevated blood creatine phosphokinase levels	16 (4.7)
Back pain	16 (4.7)

Table data are numbers (%) of patients in whom an event occurred at least 1 time during the trial

treatment with famotidine were all found to be *H. pylori*-negative [10]. Therefore, trial results reported to date are inconsistent, although *H. pylori* eradication is generally recommended in most situations [14, 16]. Besides, because it was difficult to predict the influence of rebound acid hypersecretion occurring after *H. pylori* eradication [17] on the results of the present study, the subjects who required long-term LDA therapy were not obliged to undergo *H. pylori* eradication prior to administration of the study drug, and the protocol was designed to allow patients to be treated with a PPI or *H. pylori* eradication until the day immediately before the start of treatment with lansoprazole or gefarnate, given the varying durations of prior LDA use among the patients. Thus, the study attempted to evaluate the efficacy of lansoprazole vs. gefarnate against ulcer recurrences in an ordinary clinical setting, in which *H. pylori* eradication was implemented at the discretion of the attending physician.

Analyses in both *H. pylori*-positive and -negative subgroups in the present study showed ulcer risk reductions in the lansoprazole group as compared to the gefarnate group, although the risk reduction rate was higher in the *H. pylori*-positive patients. This finding is consistent with a previous study in patients at relatively low risk for ulcer complications [8] and supports the usefulness of low-dose lansoprazole in Japan, where the prevalence of *H. pylori* infection is high [18]. Additionally, although more *H. pylori*-negative patients will need prophylactic treatment for preventing

LDA ulcers in Japan, where the *H. pylori* infection rate is predicted to gradually decrease [19], low-dose lansoprazole should still be effective in these patients as well.

A final analysis of the study data showed that lansoprazole produced a 90.1% reduction in the risk of ulcer recurrence, which was highly significant. The reduction rate is similar to that in a placebo-controlled study conducted in Hong Kong in patients taking LDA [7] and even higher than that in another study in patients with ulcers associated with LDA, where the rate of risk reduction was found to be about 70% [8].

Although the recurrence of ulcers observed by endoscopy was assessed as the primary endpoint in the present study, other clinical endpoints, such as gastrointestinal bleeding and patient hospitalization, were also compared between the treatment groups, because these true clinical outcomes are very important in evaluating the drugs for efficacy. In this study, more patients in the gefarnate group developed gastric or duodenal hemorrhagic lesions and were hospitalized with serious adverse events leading to gastric or duodenal bleeding. Thus, overall, lansoprazole was superior to gefarnate in all endpoints assessed in this study.

Furthermore, there were no new-onset ulcers noted in the additional 6 months' follow-up trial, supporting the idea that lansoprazole provides superior long-term efficacy in preventing LDA-associated gastric/duodenal ulcers, compared to gefarnate.

Of note, the present study represents the longest follow-up (18 months or more) of patients with a definite history of gastric or duodenal ulcer who required long-term LDA therapy, of all reports (3–12 months) published in the literature [7–10].

Thus, lansoprazole appears to have an important role to play in reducing the risk of gastroduodenal ulcers in patients at high risk of developing ulcers who require long-term LDA therapy due to cardiovascular and cerebrovascular disease, while at the same time allowing such antiplatelet therapy to reduce thromboembolic events in these patients.

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Cancer Risk in Diabetic Patients Treated with Metformin: A Systematic Review and Meta-analysis

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Abstract

Background: A growing body of evidence has suggested that metformin potentially reduces the risk of cancer. Our objective was to enhance the precision of estimates of the effect of metformin on the risk of any-site and site-specific cancers in patients with diabetes.

Methods/Principal Findings: We performed a search of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov for pertinent articles published as of October 12, 2011, and included them in a systematic review and meta-analysis. We calculated pooled risk ratios (RRs) for overall cancer mortality and cancer incidence. Of the 21,195 diabetic patients reported in 6 studies (4 cohort studies, 2 RCTs), 991 (4.5%) cases of death from cancer were reported. A total of 11,117 (5.3%) cases of incident cancer at any site were reported among 210,892 patients in 10 studies (2 RCTs, 6 cohort studies, 2 case-control studies). The risks of cancer among metformin users were significantly lower than those among non-metformin users: the pooled RRs (95% confidence interval) were 0.66 (0.49–0.88) for cancer mortality, 0.67 (0.53–0.85) for all-cancer incidence, 0.68 (0.53–0.88) for colorectal cancer (n = 6), 0.20 (0.07–0.59) for hepatocellular cancer (n = 4), 0.67 (0.45–0.99) for lung cancer (n = 3).

Conclusion/Significance: The use of metformin in diabetic patients was associated with significantly lower risks of cancer mortality and incidence. However, this analysis is mainly based on observational studies and our findings underscore the more need for long-term RCTs to confirm this potential benefit for individuals with diabetes.

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Introduction

Hyperinsulinemia and hyperglycemia are thought to promote carcinogenesis in patients with diabetes mellitus. Several meta-analyses have demonstrated that diabetes is associated with increased risks of site-specific cancers of the breast (1.2) [1], endometrium (2.1) [2], bladder (1.2) [3], liver (2.5) [4], colorectum (1.3) [5], and pancreas (1.8–2.1) [6,7], and also a decreased risk of prostate cancer (0.8–0.9) [8,9]. The evidence for non-Hodgkin's lymphoma remains inconclusive [10,11]. Our previous meta-analyses showed that patients with diabetes have an inscreased risk of total cancer (relative risk, 1.1–1.7) [12–14], whereas more recent studies did not [15,16]. Metformin is an insulin sensitizer that is the drug of first choice in the management of type 2 diabetes [17], given its safety profile and lower cost. Metformin reportedly has a potential anti-cancer effect by activating adenosine 5′-mono-phosphate-activated protein kinase (AMPK) in addition to alleviating hyperinsulinemia and hyperglycemia. Although other mechanisms for this risk reduction have been hypothesized, none have been elucidated entirely. Previous meta-analyses have suggested that metformin is associated with a reduced risk of cancer in diabetic subjects [18,19]. However, those analyses were based solely on a few observational studies and additional reports have been published recently.

In light of the worldwide diabetes epidemic and the higher mortalities in cancer patients with diabetes [20,21], explorations of effective cancer prevention are of clinical importance for the targeted management of diabetes in daily practice. Moreover, they are crucial in the areas of public health, since a modest increase in the risk of cancer translates into a substantial social burden. These circumstances prompted us to investigate, with greater precision, the preventive effect of metformin on cancer mortality and incidence by scrutinizing pertinent original reports including randomized controlled trials (RCTs), and combining their data in an attempt to obtain meaningful clues for the prevention of cancer in patients with diabetes [13].

Methods

Search

Searches of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov from their inception until October 12, 2011, were performed. Studies evaluating the risks of cancer mortality or incidence among diabetic patients

taking metformin, compared with those not taking metformin, were identified using a combination of the following medical subject heading terms: 'diabetes', 'metformin', 'cancer' or 'neoplasms', and 'risk' or 'risk factors'. The reference lists of the pertinent articles were also inspected.

Selection/Study Characteristics

We assessed all the identified RCTs, cohort studies, case-control studies, and cross-sectional studies on the risk of cancer based on original data analyses to determine their eligibility for inclusion in a qualitative analysis. The inclusion criteria in the meta-analysis are as follows: published full-text report in English-language, RCTs with parallel-design of metformin as a treatment of type 2 diabetes at least one year's follow-up period, observational studies of any duration in patients with type 2 diabetes, reporting relative risks, i.e. hazard ratios (HRs), RRs, or odds ratios, adjusted for possible confounders with confidence intervals (CIs). The comparators were defined as any treatment not including metformin.

Validity assessment

To ascertain the validity of the eligible studies, the quality of each report was appraised in reference to the CONSORT statement [22] and the STROBE statement [23].

Data abstraction

We reviewed each full-text report to determine its eligibility and extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the subjects (including age, sex, and other treatment), study design, published year, follow-up period, and the methods used for ascertaining the diagnosis of cancer. Study authors were contacted as needed to obtain detailed data. Any disagreement was resolved by a consensus among the investigators.

Quantitative data synthesis

If more than one study was published for the same cohort, the report containing the most comprehensive information on the population was included to avoid overlapping populations. The reports were summarized both qualitatively and quantitatively. Three articles that did not specify the case numbers were not included in the calculation of the mortality and incidence. If the metformin comparator included more than one treatment, the oral monotherapy groups were included in the analysis because these groups were deemed to be at an equivalent stage of diabetes. If an article provided the relative risks for all cancer and site-specific cancers, the all cancer data were included in the primary qualitative and quantitative analyses and the site-specific data were used in the secondary analyses performed according to cancer site. The risks for site-specific cancers were appraised if three or more qualified reports were identified for a given cancer site. Response to metformin exposure was evaluated by using linear-regression analysis.

In the meta-analysis, each adjusted relative risk was combined and the pooled RRs with the 95% CI was calculated using the random-effects model with inverse-variance weighting. Heterogeneity among the studies was evaluated using I^2 statistics. The possibility of a publication bias, which can result from the non-publication of small studies with negative findings, was assessed visually using a funnel plot for asymmetry. RevMan (version 5.1) was used for these calculations. A sensitivity analysis was performed by separating the RCTs and the observational cohort / case-control studies and the equality of RRs between RCTs and observational studies were assessed by using z-statistic tests. All the procedures were in accordance with the guidelines for the Quality of Reporting of Meta-analyses [24], the meta-analysis of observational studies in epidemiology [25] and the PRISMA statement [26].

Results

Search Results

A total of 412 articles were identified during our search; of these, 32 were assessed with respect to their eligibility for inclusion in our review, which was aimed at determining the influence of metformin on cancer mortality and incidence in patients with diabetes (**Fig. 1**). Four articles [27–30] were excluded from the systematic review because of population overlapping and four other reports were excluded because they investigated the overall survival rate [31,32], cancer incidence exclusively in patients with hepatitis C [33], and biochemical recurrence [34]. Out of these 32 articles, a total of 24 (11 observational cohort studies [35–45], 3 randomized controlled trials [46–49], and 10 case-control studies [29,50–58]) were included in the systematic review and meta-analysis. The UK Prospective Diabetes Study (UKPDS) 34 [49] involved two independent investigational trials (metformin vs. conventional therapy and sulfonylurea vs. sulfonylurea plus metformin), and these trials were included in the meta-analysis as two separate data.

Table S1 shows the characteristics of each included study according to the study design. The 24 selected articles included in the systematic review were moderately heterogeneous in terms of population demographics, study design, and the assessment of confounding factors. The diabetes sample size in these studies ranged from 361 to 998,947 patients. Of the 21,195 diabetic patients in 6 studies, 991 (4.5%) cases of cancer death were reported. A total of 11,117 (5.3%) cases of incident cancer at any site were reported among 210,892 patients in 10 studies. Major confounding factors such as cigarette smoking, alcohol intake, and hyperglycemia were not reported in several studies.

The risk of bias and the adjustment factors among the studies are summarized in **Table S2**. Diabetes was diagnosed using blood tests (n = 8), prescription databases (n = 6), medical records (n = 4), self-reports (n = 3), and health insurance database (n = 4). All the diagnoses of cancer were confirmed using valid records or registries. All the studies, except for the RCTs, adjusted the estimates for potential confounding factors. The analysis of dose-response was performed in 3 studies [38–40]. Some studies excluded the data for metformin exposure less than 1 year [50,52] or 2 years [58] to minimize bias. The effect on the total cancer risk over the follow-up period was inspected in 3 studies [40,55,58]. Direct comparison of the effect between metformin and other specific medications were reported in 2 RCTs [46–48].

Qualitative Summary

The majority of the studies included were methodologically fair in quality. Among 10 case-control studies, six were nested ones [50–52,55,56,58]. All the four cohort studies [35,38,40,41] on cancer mortality revealed a significant decrease (range, 23%–75%), and the two RCTs showed no significant effect of metformin [49]. There was no study that directly compared the risk associated with metformin vs other medications or analyzed the correlation between the follow-up length and the effect of metformin on cancer mortality. The overall correlation of the follow-up period with the mortality was nonsignificant ($r = -0.04$, $p = 0.9$). One study revealed that the HR (95% CI) for cancer mortality with every increase of 1 g metformin was 0.58 (0.36–0.93) [38].

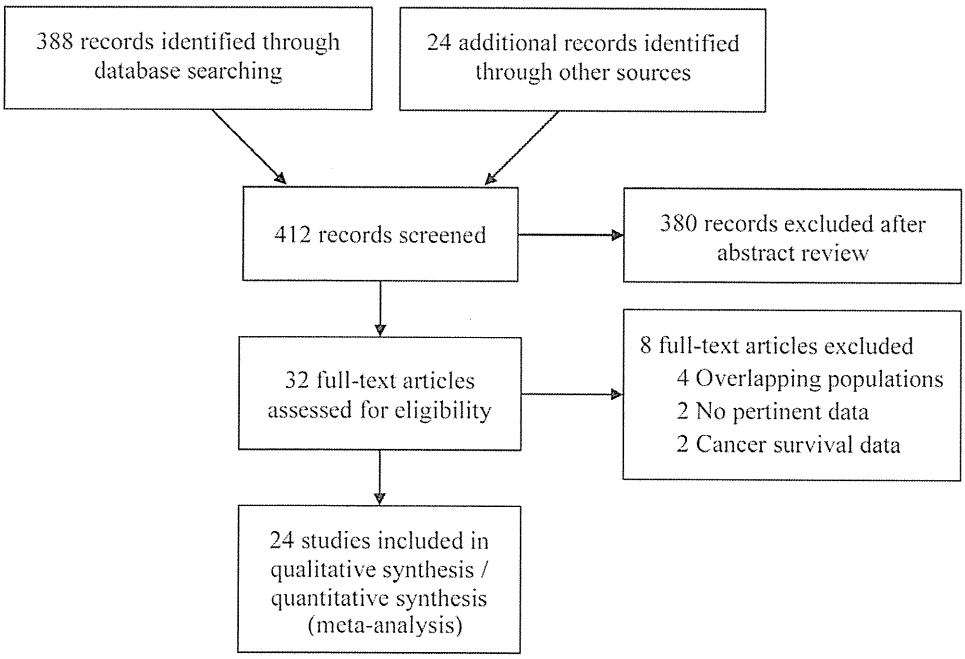

Figure 1. Flow diagram of study selection.
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Five studies (3 cohort studies [36,39,40] and 2 case-control studies [55,56]) reported a significant decrease (range, 26%–88%), the two RCTs showed no significant effect of association [46–48] and none demonstrated a statistically significant increase in the risk of all-cancer incidence among metformin users. The cancer risk for metformin users was not significantly different from that for rosiglitazone or sulfonylurea users in RCTs [46–48]. One cohort study showed a trend for metformin users to have a higher risk of cancer in the first 2 years of follow-up. The beneficial effect of metformin on the risk of total cancer incidence was exposure-dependent in 2 case-control studies [55,56]. The overall correlation of the follow-up period with the incidence was nonsignificant ($r = -0.32$, $p = 0.4$). One study reported that its effect on cancer incidence was dose-dependent (p for trend <0.05) [39] suggesting that the minimal effective dose can be 500 mg /day, while the other showed no significant differences among doses [40].

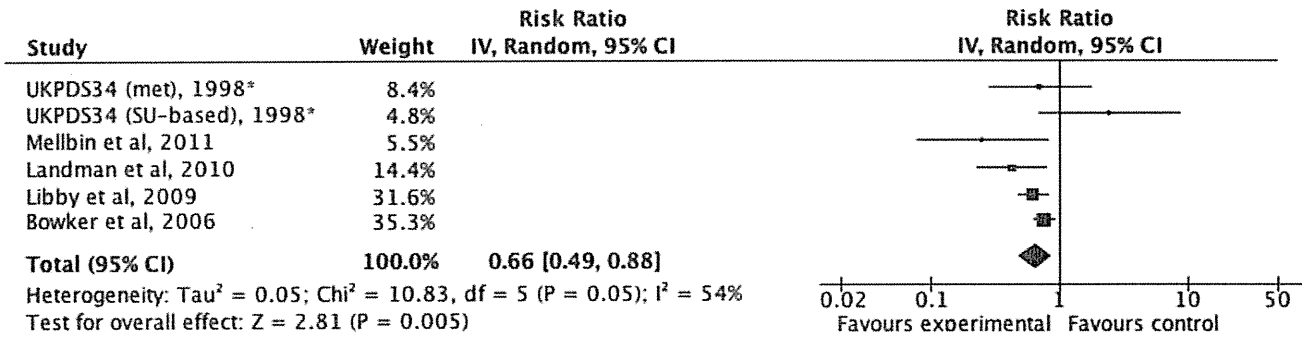
Among the studies evaluating the risks of site-specific incident cancers in patients with diabetes who were taking metformin, more than two studies (including subgroup analyses) recognized significantly reduced risks for cancers of the pancreas [36,39,54], colorectum [36,39,40], and liver [29,39,53], and none showed a significantly increased risk of a site-specific cancer. All these risk decrements were moderate (RR range, 0.06–0.60). Of note, no significant increases or decreases in the risk of cancers of the breast, prostate or stomach were reported, except for a significant decrease in the risk of prostate cancer in one report [42] and breast cancer in another [52]. The number of studies examining other cancer sites was two or fewer, and these studies were not reviewed in the present analysis.

Quantitative Summary (Meta-analysis)

Based on the quality appraisal in our systematic review, a total of 24 articles that provided sufficient information were included in the meta-analysis (**Fig. 1**). **Fig. 2** illustrates the significantly decreased risks of all-cancer mortality and incidence in metformin-users, compared with non-metformin users. In a sensitivity analysis, the pooled estimate (95% CI) for all-cancer mortality among the observational cohort studies was 0.62 (0.46–0.82), $I^2 = 56\%$, $p = 0.08$ and the estimate among the RCTs was 1.22 (0.36–4.11), $I^2 = 60\%$, $p = 0.12$. The difference in the RRs between the observational studies and the RCTs was not statistically significant ($p = 0.35$). The pooled RR (95% CI) for all-cancer incidence among the observational cohort studies was 0.66 (0.49–0.88), $I^2 = 96\%$, $p<0.00001$, the pooled RR among the case-control studies was 0.38 (0.23–0.61), $I^2 = 3\%$, $p = 0.31$ and the estimate among the RCTs was 1.03 (0.82–1.31), $I^2 = 30\%$, $p = 0.23$. The difference in the RRs between the observational studies and the RCTs was statistically significant ($p = 0.019$). As summarized in **Fig. 3 and Fig. 4**, the incident cancer risks were also significantly decreased for cancers of the colorectum, liver and lung. The RRs of prostate cancer, breast cancer, pancreatic cancer and gastric cancer were not statistically significant. Significant heterogeneity was observed in the majority of these analyses. No apparent publication bias was apparent, as assessed using a funnel plot (**Fig. S1**).

Discussion

Our systematic review and meta-analyses of worldwide reports demonstrated that metformin is associated with a substantially lower risk of all-cancer mortality and incidence, compared with other treatments for diabetes. They also showed that metformin significantly reduced the risks of cancers of the colorectum, liver and lung. These findings support the hypothesis that metformin potentially has an anti-cancer effect. In light of the fact that cancer is the second and diabetes the twelfth leading cause of death worldwide [59] and that the number of people with diabetes is rapidly increasing, our findings have substantial clinical and public implications on a global scale and point to the need for the further investigation of the anti-cancer mechanism of metformin and for long-term RCTs to confirm this clinical benefit.



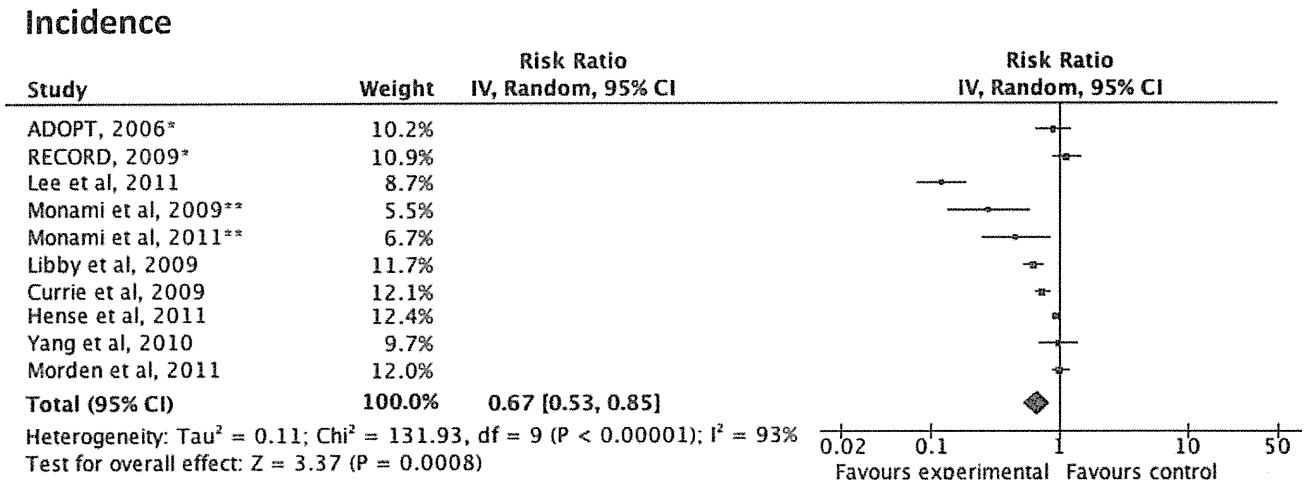


Figure 2. Adjusted risk ratios for all-cancer mortality and incidence among subjects with diabetes taking metformin. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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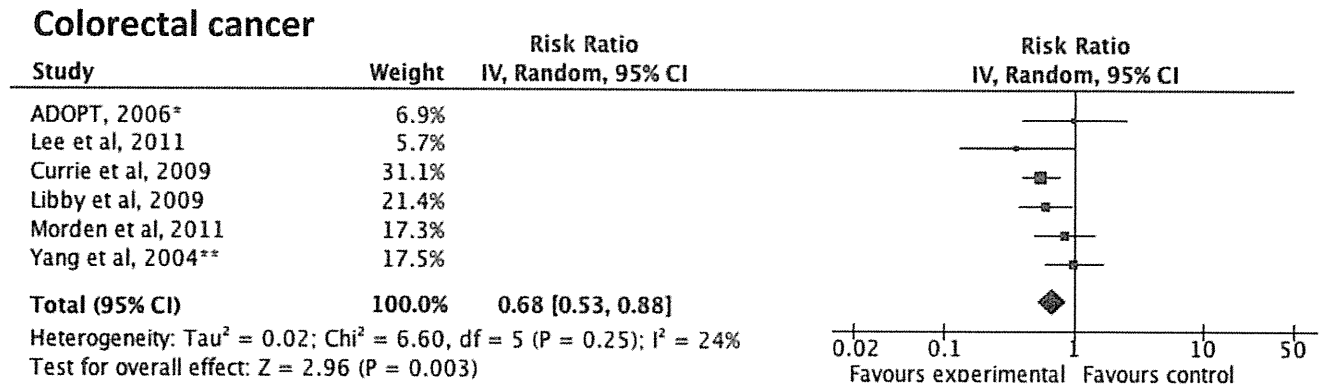
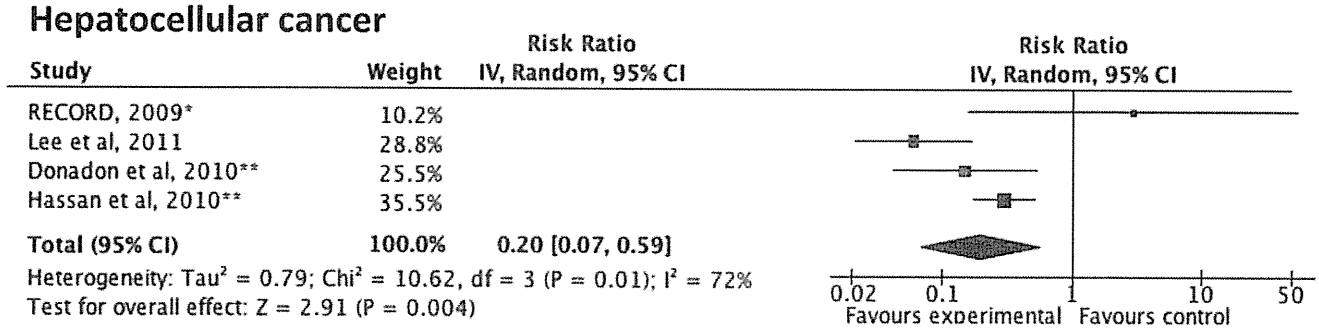
The strength of our present study is that the analysis was mainly based on large population-based data originating from multiple nations and was performed with a high level of precision. Compared with recently published studies [18,19], our updated study is novel in that data from RCTs were incorporated and cancer risks for substantially more sites were analyzed. Although the significantly decreased pooled RRs for all-cancer mortality / incidence and cancer at most sites were robust, the results of the component studies were statistically heterogeneous. Of note, all the individual and pooled results of the RCTs were neutral. It seems that each follow-up period in these RCTs is similar to many others in the observational studies and they have power enough to detect the differences in cancer risk. In the analysis of cancer mortality, there was no significant difference in RR between the RCTs and the observational studies. For cancer incidence, on the other hand, the overall RR was significantly reduced but the difference was statistically significant. This discordance may imply that the apparent anti-cancer effect of metformin in observational studies was affected by confounding biases and thus more RCTs are awaited to clarify the effect of metformin on cancer incidence. The large I^2 values indicated that the range of the plausible risk estimates was wide but no evidence in our analysis suggested that metformin may increase the risk of cancer. These findings may reflect the different mechanisms of cancer prevention at different sites and / or different epidemiological characteristics among the diverse populations included in our study.

Evidence has been accumulating to suggest that diabetic patients have a higher risk of cancer than non-diabetic people [12,13]. While the mechanisms are yet to be investigated, insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis, as insulin may have a possible mitogenic effect via its binding to the insulin-like growth factor-1 receptor





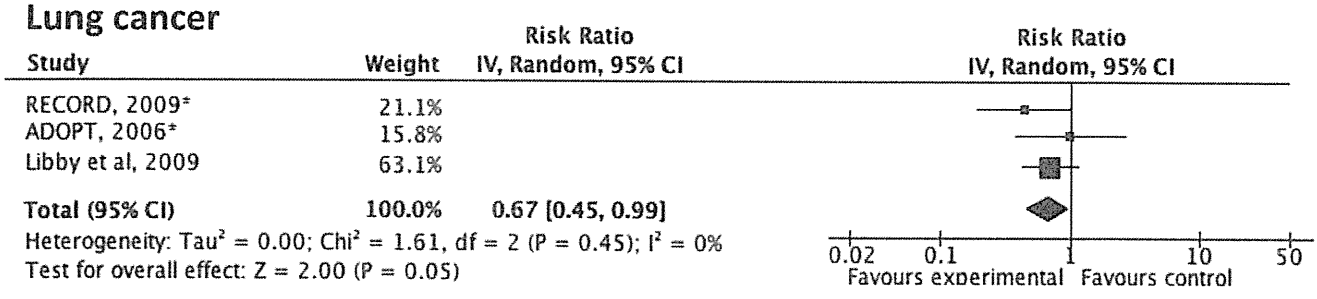


Figure 3. Adjusted risk ratios for site-specific cancer incidence among subjects with diabetes taking metformin. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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[60–70]. In addition, hyperglycemia itself may promote carcinogenesis directly [71,72] or indirectly by increasing oxidative stress [73–79]. However, these speculations are derived from retrospective observational studies and may not necessarily demonstrate causality because of possible biases and confounders, such as coexisting obesity and age [15,80,81]. In fact, more recent studies demonstrated no or minimal increments in cancer risk [15,16] and the data from insulin-treated patients are inconclusive [82]. Of interest, diabetes reportedly protects against the development of prostate cancer [8,9], since it is testosterone-dependent and testosterone deficiency is common among men with diabetes secondary to low levels of sex hormone-binding globulin (SHBG)

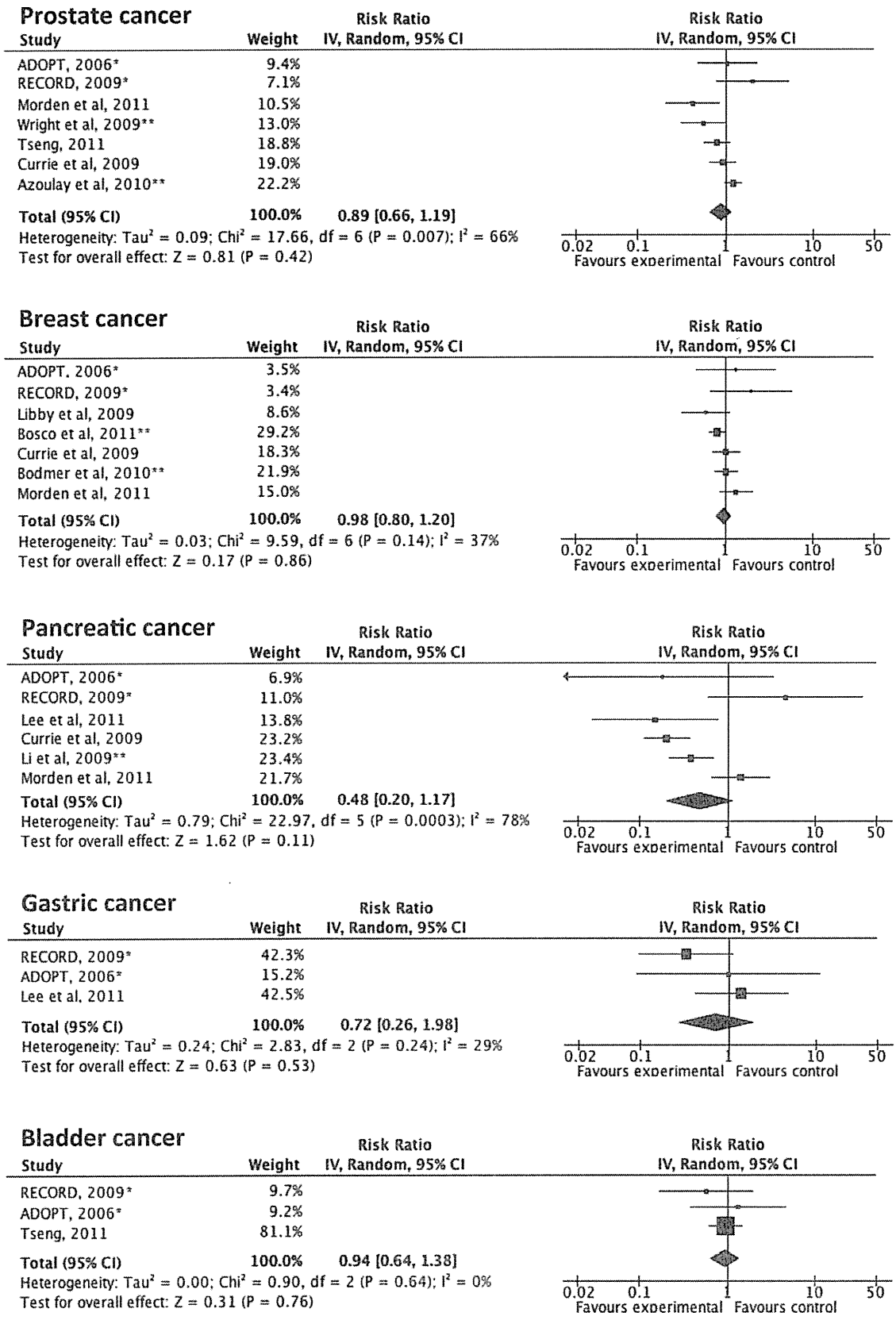

Figure 4. Adjusted risk ratios for other site-specific cancer incidence among subjects with diabetes taking metformin. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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and partially because of insulin resistance [83–85]. Low SHBG levels may facilitate the conversion of testosterone to estradiol, which in turn may result in an increased risk of hormone-dependent breast cancer.

Several mechanisms for the anti-cancer effect of metformin have been postulated, and several prospective clinical trials to evaluate its safety and efficacy are ongoing [82,86]. Indirect pathways include the prevention of weight gain and the amelioration of hyperinsulinemia, both of which may promote carcinogenesis. In addition, metformin activates AMPK through LKB-1, a tumor suppressor protein kinase. AMPK inhibits protein synthesis and gluconeogenesis during cellular stress and inhibits mammalian target of rapamycin (mTOR), a downstream effector of growth factor signaling, which is frequently activated in malignant cells. In human breast cancer cells, it reduces HER-2 protein expression by inhibiting mTOR. Metformin also induces cell cycle arrest and apoptosis and reduces growth factor signaling. Supporting the idea of these direct effects, metformin reportedly potentiated the effect of neoadjuvant chemotherapy in early-stage breast cancer [87], decreased the risk of colorectal cancer in a small randomized trial involving non-diabetic subjects [88], and was associated with a decreased cancer risk while another insulin-sensitizer, thiazolidinedione, were not [18,54, 89,90].

Our research revealed that metformin use is associated with reduced mortality and incidence of cancer at any site, supporting the general applicability of the proposed anti-cancer mechanisms. The anti-cancer effect of metformin may also be applicable to diabetic Asians, who are generally lean and insulinopenic [12], given the fact that they have a higher cancer risk than non-diabetic Asians [12–14] and the data for Asians [39] were in line with the results of our meta-analyses. On the other hand, the magnitude of the risk reduction varies among site-specific cancers. This variance in efficacy may result from differences in carcinogenesis at certain sites. For instance, elevated levels of insulin and glucose may exert an important influence in the development or growth of epithelial malignant tumors of the colon [91–93], pancreas [94,95], and breast [96], and metformin may prevent incident colon cancer in non-diabetic subjects [88]. An animal study suggested that metformin prevented smoking-related lung cancer in mice, probably by inducing some hormone from the liver [97]. With regard to sex hormone-dependent cancers, the effect of metformin on the development of prostate cancer and breast cancer in our analysis was neutral. Metformin improves insulin sensitivity, thereby possibly raising the testosterone level. This may have promoted prostate cancer development and may have diluted the beneficial effect of metformin. In fact, one cohort study reported no benefit of metformin in terms of the biochemical recurrence rate after radical prostatectomy in diabetic patients [34]. The nonsignificant pooled RR for breast cancer may have resulted from the diversity in confounder adjustments and follow-up periods: some analyses were not fully adjusted for risk factors, including the menopause status, and one study suggested that only long-term exposure to metformin reduced the risk of breast cancer [51]. The fact that one preliminary study suggested a promising effect of metformin on pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer [87] may point to the possibility that metformin simply augmented the efficacy of chemotherapy for breast cancer [18,86]. Further detailed studies to analyze the interaction between carcinogenesis and the action of metformin, and to evaluate its effect for nondiabetic people are eagerly awaited.

Limitations

Our analysis should be interpreted in the context of the following limitations. First, the relation may not necessarily be causal, particularly in the observational studies [80], because of possible confounding factors and biases that may not have been fully adjusted for in this study: some risk factors such as cigarette smoking, alcohol intake, and hyperglycemia were not specified in several studies, which may have rendered the results less valid. Few studies demonstrated the dose-response to support biological plausibility. Confounding by treatment indication [98], which may have been minimizes by using propensity-score matching analysis, might overestimate the effect of metformin: the presence of such pre-existing conditions as older age and liver disease precludes metformin usages and thus, metformin users may be generally younger and at lower risk of cancer than in those in comparator groups. Only a few observational studies analyzed the effects over time and thus protopathic bias (i.e. early cancer leading to unstable diabetes and hyperglycemia, with patients switching diabetes treatment) [15] may remain moderate. In fact, the individual and pooled estimates from the RCTs were all neutral; the estimates comparing with other medication were neutral, as well. For all these limitations, however, observational studies provide the good available evidence regarding potential treatment effects / harms and the overall pooled estimates were robust. Moreover, evidence has been accumulating to support causality, both clinically and biochemically, as discussed earlier. Secondly, it is also important to realize that the populations of the studies were heterogeneous, most likely because of the diversity of the study designs and ethnicities, and that the sensitivity of each site-specific cancer to metformin may vary. Lack of the standardized treatment protocol in the descriptive studies might explain the observed associations: the possibility that other diabetes treatments may increase the risk of cancer may have resulted in an overestimation of the effect of metformin. Lack of the standardized diagnostic procedures for cancer may have caused detection bias in some cases. Even with these limitations, our analysis supports oncogenic safety of metformin and it should provide physicians with an additional incentive to pay integrated clinical attention and elucidate the complex interactions between diabetes treatment and cancer.

Conclusions

Our meta-analysis favors the oncogenic benefit of metformin for diabetic patients. However, observational studies were moderately heterogeneous and biased, and RCTs did not show a significant effect. Our findings underscore the need for long-term randomized prospective studies to confirm this potential benefit.

Supporting Information

Figure S1 Funnel plot of the included studies.
(TIFF)

Table S1 Study characteristics.
(DOC)

Table S2 Quality assessments of the included studies.
(DOC)

Checklist SI PRISMA Checklist.
(PDF)

Author Contributions

Conceived and designed the experiments: HN MN. Performed the experiments: HN AG TT. Analyzed the data: HN AG TT. Contributed reagents/materials/analysis tools: HN AG TT. Wrote the paper: HN. Reviewed/edited the manuscript: AG TT MN.

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Modification of the Trauma and Injury Severity Score (TRISS) Method Provides Better Survival Prediction in Asian Blunt Trauma Victims

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Abstract
Background The objective of the present study was to identify logistic regression models with better survival prediction than the Trauma and Injury Severity Score (TRISS) method in assessing blunt trauma (BT) victims in Japan and Thailand. An additional aim was to demonstrate the feasibility of probability of survival (Ps) estimation without respiratory rate (RR) on admission, which is often missing or unreliable in Asian countries.
Methods We used BT patient data ($n = 15{,}524$) registered in the Japan Trauma Data Bank (JTDB, 2005–2008). We also extracted data on BT patients injured in the Khon Kaen District between January 2005 and December 2008 ($n = 6{,}411$) from the Khon Kaen Hospital Trauma Registry. For logistic regression analyses, we chose the Injury Severity Score (ISS), age year (AY), Glasgow Coma Scale (GCS) score, systolic blood pressure (SBP), RR, and their coded values (c) as explanatory variables, as well as the Revised Trauma Score (RTS). We estimated parameters by the method of maximum likelihood estimation, and utilized Akaike's Information Criterion (AIC), the area under the receiver operating characteristic curve (AUROCC), and accuracy for model comparison. A model having the lower AIC is considered to be the better model.
Results The AIC of the model using AY was lower than that of the model using the coded value for AY (cAY) (used by the TRISS method). The model using ISS, AY and cGCS, cSBP, and cRR instead of the RTS demonstrated the lowest AIC in both data groups. The same trend could be observed in the AUROCCs and the accuracies. In the Khon Kaen data, we found no additional reduction of the AIC in the model using the cRR variable compared to the model without cRR.
Conclusions For better prediction of Ps, the actual number of the AY should be used as an explanatory variable instead of the coded value (used by the TRISS method). The logistic regression model using the ISS, AY, and coded values of SBP, GCS, and RR estimates the best prediction. Information about RR seems to be unimportant for survival prediction in BT victims in Asian countries.

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Introduction

The Trauma and Injury Severity Score (TRISS) [1, 2] is a standard method for estimating survival and is often used in evaluating the quality of trauma care. It provides the probability of survival (Ps) by the logistic regression model with the predictor variables of the Injury Severity Score (ISS) [3], Revised Trauma Score (RTS) [4], and categorized data (coded value) of age year (cAY). The formula is:

$$\text{logit}(\text{Ps}) = \text{Intercept} + \beta\text{ISS}^{*}\text{ISS} + \beta\text{RTS}^{*}\text{RTS} + \beta\text{cAY}^{*}\text{cAY}$$

logit is the link function of the logistic regression model and represents the natural logarithm of the odds of the probability (Ps) of a positive outcome (survival/death). The

intercept and coefficients are determined by versions of the Abbreviated Injury Scale (AIS) [5, 6] required for ISS calculation. The RTS is calculated using the Glasgow Coma Scale (GCS) score, the systolic blood pressure (SBP), and the respiratory rate (RR). The formula is a linear equation of their coded values (c):

$$RTS = 0.9368^{*}cGCS + 0.7326^{*}cSBP + 0.2908^{*}cRR.$$

However, in our previous study [7], we demonstrated that logistic regression models with direct use of the actual AY provide a better fit than the TRISS model using the categorized (coded) AY, because a rapid increase in mortality is not observed around the AY of 55 in Japan. Moreover, a model without the RR information can be made with only a slight reduction in accuracy, and it can be feasible for Ps prediction if the RR data are missing.

This study aimed to modify the TRISS model in order to obtain better survival prediction for blunt trauma (BT) victims in Japan and Thailand, and to pursue the possibility of Ps estimation without RR information on admission.

Methods

Study design, population, and settings

We conducted a retrospective observational study to create Ps prediction models for BT victims in Japan and in Thailand. The protocol of the study was approved by the ethics committee of the National Center for Global Health and Medicine.

Once approval was obtained from the Trauma Registry Committee of the Japanese Association for the Surgery of Trauma, we used deidentified anonymous data from the JTDB [8], with which 144 Japanese hospitals have been involved since 2004. From 2005 to 2008, 25,310 patients who had suffered BT were registered in the JTDB. For analyses, we collected data on 15,524 patients without missing both outcome information on survival and information on the predictors for Ps calculation by the TRISS method using the 1990 revision of AIS (AIS90) [5].

From 2005 to 2008, 6,667 patients who had experienced BT in the Khon Kaen District in Thailand were registered in the Khon Kaen Regional Hospital Trauma Registry, where data have been collected since 1997. The hospital is one of the World Health Organization (WHO) collaborating centers for injury prevention and safety promotion, and has been providing outstanding contributions. With the permission of the hospital, we analyzed data on 6,411 patients, including items necessary for Ps calculation by the TRISS method using the 1985 version of the AIS (AIS85) [6] and information on survival at discharge.

Analyses

We performed logistic regression analyses in order to establish models. Maximum likelihood estimation was used as the method of coefficient estimation for each model. In addition to the RTS, AY, ISS, GCS, SBP, and RR, we used their coded values (cAY, cGCS, cSBP, cRR), defined in Table 1, as predictor variables. The outcome variable was survival (=1) with non-survival (=0) at discharge. We used the likelihood ratio χ^2 test for evaluating independence of variables. The statistically significant level was considered to be <0.05.

For model selection, we used Akaike's Information Criterion (AIC) [9], defined as:

$$AIC = -2^{*}\log(\text{maximum likelihood}) + 2^{*}(\text{number of adjusted parameters}).$$

Table 1 Demographics of each data set and distribution of variables

	Coded value	JTDB data	Khon Kaen data
Number		15,524	6,411
Gender (male %)		69.2	74.1
Age (years) mean (SD)		48.5 (23.2)	31.6 (18.9)
<55	0	55.0%	87.6%
≧55	1	45.0%	12.4%
RTS mean (SD)		6.78 (2.13)	7.47 (1.08)
SBP			
>89 mmHg	4	86.3%	95.9%
76–89 mmHg	3	3.2%	1.6%
59–75 mmHg	2	2.4%	1.1%
1–49 mmHg	1	1.3%	0.2%
No pulse	0	6.8%	1.2%
GCS score			
13–15	4	73.8%	89.4%
9–12	3	7.3%	3.0%
6–8	2	5.9%	4.6%
4–5	1	2.2%	1.1%
<4	0	10.8%	1.9%
RR			
10–29/min	4	77.9%	92.1%
>29/min	3	14.3%	0.2%
6–9/min	2	0.4%	0.02%
1–5/min	1	0.2%	0.2%
0/min	0	7.2%	7.5%
ISS mean (SD)		17.9 (13.6)	9.5 (10.1)
Survival (%)		85.0	95.9

JTDB Japan Trauma Data Bank, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *SBP* systolic blood pressure, *GCS* Glasgow Coma Scale score, *RR* respiratory rate

The AIC was used to identify the model that best explains the data with a minimum of free parameters. The model having the lower AIC is considered to be the better model.

We compared the area under the receiver operating characteristic curve (AUROCC) (which distinguishes between survival and non-survival, and varies between 0.5 and 1 [1 = perfect discrimination]), and accuracy (the proportions of survivors with Ps $\geq$ 0.5 and proportions of non-survivors with Ps $<$ 0.5) among the models.

The JMP 9.0 (SAS Institute Inc., Cary, NC) and SAS 9.1 (SAS Institute Inc., Cary, NC) software packages were used for statistical analyses.

Results

Table 1 shows the demographics of each data set, including the distributions of predictor variables and the proportions of survivors. The JTDB seems to have data of older and more severely injured BT patients than the Khon Kaen Trauma Registry. The proportions of patients whose RRs were more than 29/min or 6–9/min were quite low in the Khon Kaen data.

The survival proportion of younger patients (AY $<$ 55, cAY = 0) was 88.13%, which was slightly higher than the survival proportion (81.25%) of the older patients (AY $\geq$ 55, cAY = 1) in the JTDB data. In the Khon Kaen data, the difference can hardly be recognized between the survival proportion (95.86%) of the older patients (AY $\geq$ 55, cAY = 1) and the survival proportion (95.92%) of the younger patients (AY $<$ 55, cAY = 0).

Table 2 shows the AIC of each model. The AIC of the model using AY was lower than that of the model using cAY (used by the TRISS method). In both data groups, the model using ISS, AY and cGCS, cSBP, and cRR instead of the RTS demonstrated the lowest AIC, 4,305 and 1,105, respectively. In the Khon Kaen data, no additional reduction of the AIC was shown in the model with the cRR variable compared with the model without cRR.

The estimated coefficients of the logistic regression models derived from the JTDB data are shown with the original TRISS coefficients in Table 3. As discussed in previous reports [10], each coefficient of cSBP, cGCS, and cRR on the TRISS line of the table is obtained by multiplying by the coefficient of RTS, namely 0.8085, in the TRISS equation using the AIS90. All estimated coefficients were significant. However, the intercept of the model using the ISS, AY, cSBP, and cGCS was not significant.

Table 2 AIC for each model

Regression model	AIC Japan	AIC Khon Kaen
ISS, RTS, cAY	4,372	1,120
ISS, RTS, AY	4,305	1,109
ISS, AY, cSBP, cGCS, cRR	4,305	1,105
ISS, AY, cSBP, cGCS	4,347	1,105

Regression models are represented by their predictor variables

AY age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

Table 3 Coefficients of logistic regression models of Japanese data

Regression model	Intercept	βISS	βRTS	βAY	βcAY	βcSBP	βcGCS	βcRR
TRISS (AIS90)	−0.4499	−0.0835	0.8085	×	−1.743	0.5923	0.7574	0.2351
ISS, RTS, cAY	−1.9502*	−0.0679*	1.0096*	×	−1.492*	×	×	×
	(0.1812)	(0.00310)	(0.024)		(0.086)			
	[115.85]	[479.6]	[1,723]		[297.6]			
ISS, RTS, AY	−0.76266*	−0.0710*	1.0256*	−0.0379*	×	×	×	×
	(0.2011)	(0.00316)	(0.024)	(0.00198)				
	[14.38]	[504.7]	[1,718]	[367.1]				
ISS, AY, cSBP, cGCS, cRR	−1.0723*	−0.0711*	×	−0.0383*	×	0.7370*	0.9318*	0.4243*
	(0.2616)	(0.00317)		(0.00199)		(0.0496)	(0.0281)	(0.0604)
	[16.79]	[502.2]		[369.9]		[221.2]	[1096.9]	[49.3]
ISS, AY, cSBP, cGCS	−0.3375	−0.0707*	×	−0.0369*	×	0.9017*	0.9814*	×
	(0.2059)	(0.00314)		(0.00196)		(0.0410)	(0.0273)	
	[2.69]	[508.6]		[354.4]		[483.3]	[1,290]	

Regression models are represented by their predictor variables

β regression coefficients

AIS abbreviated injury scale, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *AY* age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

* $p < 0.05$ (standard error) [χ^2 value]

The estimated coefficients of the logistic regression models derived from the Khon Kaen data are shown with the original TRISS coefficients in Table 4. Each coefficient of cSBP, cGCS, and cRR is obtained by multiplying by 0.9544, that is, the coefficient of RTS of the TRISS equation using the AIS85. The variable of cRR had a very low χ^2 value, and was not significant ($p = 0.06$). The intercepts of the models using ISS, AY, cSBP, and cGCS with or without cRR were not significant.

All models, including the models without the cRR variables, had AUROCCs > 0.95 in both data sets (Table 5). The model using AY, ISS, and RTS provided better AUROCC than the model with the variables of cAY, ISS, and RTS in both groups of data.

Discussion

Tables 3 and 4 reveal that the χ^2 value of cAY is much smaller than that of AY. Therefore, categorization (coding) of AY with a cut-off value of 55 reduces the amount of information and the discriminative abilities in both countries. This seems to be due to no obvious increase in mortality above the AY of 55 in the registry data of both Japan and Thailand, unlike that seen in the Major Trauma Outcome Study (MTOS) of the United States, from which the TRISS model was derived [1, 2]. Thus, we recommend the use of AY instead of cAY as a predictor variable in Asian countries. From the results of their M-statistic score calculation, Fujita et al. [11] concluded that the trauma population of a particular trauma center in Tokyo that has been participating in the JTDB differed significantly from that of the MTOS. Fujita et al. pointed out that modified TRISS coefficients should be adapted for outcome assessment based on the location of the injured population.

Our previous study [7] revealed that information on RR was missing in up to 18.8% of the JTDB data (2004–2007). In applying the model using only ISS, AY, cSBP, and cGCS, the Ps could be estimated in 38.1% of the patient data from which Ps was not calculated by the TRISS method. The model had sufficiently high discriminative ability (AUROCC = 0.923). Bouamra et al. [12] reported that a successful model (AUROCC = 0.947) using only GCS instead of RTS dramatically reduced the number of missing cases in the United Kingdom. However the equation of Bouamra et al. was more complicated than that of the TRISS method. Our recent study [13] demonstrated that simpler models using cGCS or cSBP with cAY and maximum AIS (or its coded value) showed high AUROCCs of >0.94, which seems to be suitable in more resource-constrained countries.

We found no additional reduction of the AIC in the model using cRR than the model without cRR in the Khon Kaen data. Moreover, multivariate analysis failed to show cRR as an independent predictor variable (Table 4). Information bias about collecting RR data might exist in

Table 4 Coefficients of logistic regression models of Khon Kaen data

Regression model	Intercept	βISS	βRTS	βAY	βcAY	βcSBP	βcGCS	βcRR
TRISS (AIS 85)	−1.2470	−0.0768	0.9544	×	−1.9052	0.6992	0.8941	0.2775
ISS, RTS, cAY	−0.7241	−0.0710*	0.8128*	×	−0.583*	×	×	×
	(0.3502)	(0.00548)	(0.0487)		(0.2509)			
	[4.27]	[168.2]	[278.5]		[5.40]			
ISS, RTS, AY	−0.2377*	−0.0707*	0.8215*	−0.0184*	×	×	×	×
	(0.3741)	(0.00550)	(0.0489)	(0.00463)				
	[0.4038]	[165.3]	[281.8]	[15.74]]				
ISS, AY, cSBP, cGCS, cRR	−0.1130	−0.0710*	×	−0.0177*	×	0.4458*	0.9669*	0.0960
	(0.4738)	(0.00562)		(0.00469)		(0.1019)	(0.0828)	(0.0606)
	[0.0569]	[159.8]		[14.29]		[19.13]	[136.4]	[2.515]
ISS, AY, cSBP, cGCS	−0.1565	−0.0731*	×	−0.0174*	×	0.4392*	1.0525*	×
	(0.4747)	(0.00546)		(0.00469)		(1.843)	(282.4)	
	[0.1087]	[179.0]		[13.80]		[18.43]	[282.4]	

Regression models are represented by their predictor variables

β regression coefficients

AUROCC area under receiver-operating characteristic curve, *AIS* abbreviated injury scale, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *AY* age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

* $p < 0.05$ (standard error) [χ^2 value]

Table 5 AUROCC and accuracy of models

Regression model	AUROCC Japan	Accuracy Japan (%)	AUROCC Khon Kaen	Accuracy Khon Kaen (%)
TRISS (USA)	0.9625	92.74	0.9628	96.33
ISS, RTS, cAY	0.9598	94.16	0.9657	96.60
ISS, RTS, AY	0.9624	94.38	0.9666	96.56
ISS, AY, cSBP, cGCS, cRR	0.9624	94.37	0.9667	96.66
ISS, AY, cSBP, cGCS	0.9617	94.25	0.9667	93.77

Regression models are represented by their predictor variables

AUROCC area under receiver-operating characteristic curve, *AIS* abbreviated injury scale, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *AY* age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

the Khon Kaen Trauma Registry, because the proportions of patients whose RR was >29/min or 6–9/min were quite small (Table 1). Thus, utilization of the model without cRR is recommended. In the model without cRR, the intercept can be zero for simplification because it was not statistically significant (Tables 3 and 4).

Finally, we should mention the limitations of the present study. Because of large amount of missing data for the TRISS predictors and outcome in the JTDB data, we could develop the models using 61.3% from registered BT patients. Recently, Tohira et al. [14] revealed that only 58.2% of the registered data of the JTDB from 2004 to 2008 had sufficient data on the TRISS Ps estimation and outcome, and that statistically significant differences existed in mean AY (74.8 vs. 51.2), in mean RTS (6.90 vs. 6.68), and in mean ISS (15.1 vs. 17.3) between outcome missing data and non-outcome missing data. They pointed out that selection bias may exist in research outputs gained from the extracted data from the JTDB by excluding patients with missing outcome and the TRISS predictors. However, we could demonstrate almost the same results with the Khon Kaen Trauma Registry data, which are substantially different from the JTDB in AY, RTS, and ISS. Thus, the assumable selection bias might not be important for interpretation of the results. At present, the tendency of the logistic regression models revealed in this study is observed only in the JTDB and the Khon Kaen Trauma Registry in Thailand. For generalization, our results must be verified by data from other Asian countries.

The JTDB has been using the AIS 90 [5], and The Khom Kaen trauma registry has been using the AIS 85 [6]. Both of these are out of date and insufficient for contemporary coding of injuries. Japan and Thailand has been preparing for utilization of AIS 2005 update 2008 [15], but implementation of nationwide coding under that version is not realized in either country. In the future, we should conduct this kind of research once again under the newest measure for quality assurance of our results.

Conclusions

For better prediction of Ps, the real number of AY should be used as a predictor variable instead of the coded value of AY in the TRISS method. The logistic regression model with the predictor variables of ISS, AY, and the coded value of SBP, GCS, and RR estimates the best prediction.

Information about RR seems to be less important for BT victims in Asian countries than in the United States, where the TRISS method was developed. The logistic regression model without cRR can provide the Ps with almost the same discriminative ability as the model that uses RR.

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Conflict of interest None.

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Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in East Asians

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