Influence of the ABO Blood Group on the Prognostic Value of Host-related Factors for Renal Cell Carcinoma

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We investigate associations between the ABO blood group, prognostic factors, and recurrence in renal cell carcinoma. In whole population analyses, symptomatic tumors, large tumor size, advanced tumor stage, high nuclear grade, impaired Eastern Cooperative Oncology Group performance status, low body mass index, a low peripheral blood lymphocyte count, a high neutrophil-to-lymphocyte ratio, and an elevated C-reactive protein level were significantly associated with recurrence. In subpopulation analysis by ABO blood groups (O vs. non-O), tumor-related factors (tumor size, tumor stage, and nuclear grade) were associated with recurrence in patients with both O and non-O blood groups. However, host-related factors were significantly associated with recurrence in patients with non-O blood groups but not in patients with the O blood group (decreased body mass index \( P = .006 \) vs .916), decreased peripheral blood lymphocyte count \( P = .010 \) vs .976), increased neutrophil-to-lymphocyte ratio \( P = .021 \) vs .405), and an elevated C-reactive protein level \( P = .005 \) vs .542). The peripheral blood lymphocyte count was an independent predictor of recurrence for patients with non-O blood groups. In conclusion, the prognostic value of host-related, but not tumor-related, factors for renal cell carcinoma recurrence might vary according to the ABO blood group.

Keywords: renal cell carcinoma, recurrence, ABO blood group, and prognostic factors

INTRODUCTION

Individuals with non-O blood types have been shown to have a higher risk of gastric and pancreatic cancers than those with the O blood type (Edgren et al., 2010; Wopin et al., 2009). In addition, women with non-O blood types were reported to have a significantly increased risk of developing renal cell carcinoma (RCC) (Joh et al., 2012). Further, in patients with RCC, the O blood type is associated with a better prognosis than the non-O blood types (Kaffenberger et al., 2012). However, the exact mechanism of this association remains unclear. Accordingly, we evaluated the association between ABO blood groups and prognosis in Japanese patients with RCC. Interestingly, we found that the prognostic relevance of several host-related factors differed according to the ABO blood type (O versus non-O).
MATERIALS AND METHODS

This study was approved by the institutional ethics committee. Records of 482 patients who underwent primary tumor surgical resection for RCC at our institution between 1990 and 2009 were retrospectively reviewed. Of these, 420 patients with non-metastatic RCC were included, to be consistent with the study population in the study by Kaffenberger et al. (Kaffenberger et al., 2012). Peripheral blood samples were obtained at the time of hospitalization. Tumors were staged according to the 2010 TNM Classification of Malignant Tumours staging system. Follow-up evaluations included physical examination, blood evaluation, and chest radiography every 3 months and computed tomography every 6 months. Other radiologic studies were conducted when necessary.

Data are expressed as mean ± standard deviation. The endpoint was recurrence. Recurrence-free survival (RFS) was calculated from nephrectomy to radiological detection of recurrence. The factors analyzed were age, gender, presentation mode, tumor size, tumor stage, nuclear grade, Eastern Cooperative Oncology Group performance status (ECOG-PS), body mass index (BMI), C-reactive protein level (CRP), peripheral neutrophil count, peripheral lymphocyte count (PBL), and neutrophil-to-lymphocyte ratio (NLR). Variables in the 2 groups were compared using Pearson’s chi-squared test or analysis of variance. The Cox proportional hazard model was used to assess the association between the ABO blood group, RFS, and clinicopathological variables. Age, tumor size, BMI, neutrophil count, lymphocyte counts, and NLR were considered continuous variables in Cox regression analysis. Significant variables in univariate analyses were entered into Cox multivariate analysis. Cox multivariate analysis was performed with forward stepwise variable selection. The survival curves were constructed using the Kaplan–Meier method and analyzed using the log-rank test. P values were two-tailed, and P < .05 was considered statistically significant. Statistical analyses were performed using Stata Version 12 (StataCorp LP, Texas, USA).

RESULTS

During a median follow-up period of 59 months (interquartile range [IQR], 26–107), disease recurrence was noted in 78 patients at a median of 27 months (IQR, 10–80). The site of recurrence was the lung in 43 cases, the bone in 9, the liver in 5, the brain in 4, the lymph nodes in 3, and others in 14. The 5-year and 10-year RFS rates for the whole population were 85.3% and 73.1%, respectively. Univariate analyses showed that symptomatic tumors, advanced tumor stage, high nuclear grade, impaired ECOG-PS, low BMI, a low PBL count, a high NLR, and an elevated CRP level were significantly associated with recurrence. In multivariate analysis, tumor stage and nuclear grade were independent predictors of recurrence.

For subpopulation analysis, patients were divided into 2 groups according to the ABO blood type (O vs non-O). Clinicopathological factors were not associated with the ABO blood type, and the RFS rate did not differ significantly between patients with O and non-O blood groups (Table 1). Subpopulation analysis indicated a
Table 2. Results of univariate and multivariate analyses.

<table>
<thead>
<tr>
<th></th>
<th>age</th>
<th>gender</th>
<th>presentation</th>
<th>tumor size</th>
<th>Histology</th>
<th>pT stage</th>
<th>nuclear grade</th>
<th>ECOG-PS</th>
<th>BMI</th>
<th>Neutrophil</th>
<th>Lymphocyte</th>
<th>NLR</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>continuous</td>
<td>M vs. F</td>
<td>incidental vs symptomatic</td>
<td>continuous</td>
<td>clear vs. non-clear</td>
<td>continuous (kg/m²)</td>
<td>continuous (× 10⁹/µL)</td>
<td>continuous (× 10⁹/µL)</td>
<td>continuous (rage 0.1–3 mg/dL vs. &lt;0.1 mg/dL)</td>
<td></td>
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</tr>
<tr>
<td>univariate</td>
<td>p value</td>
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<td>p value</td>
</tr>
<tr>
<td>all cases</td>
<td>0.356</td>
<td>0.146</td>
<td>0.939</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.008</td>
<td>0.001</td>
<td>0.049</td>
<td>0.012</td>
<td>0.282</td>
<td>0.211</td>
<td>0.012</td>
<td>0.096</td>
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<tr>
<td>O-type</td>
<td>p value</td>
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</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.079</td>
<td>0.001</td>
<td>1.758 (1.342–2.408)</td>
<td>2.740</td>
<td>1.928</td>
<td>0.539</td>
<td>0.317–0.917</td>
<td>0.023</td>
<td>0.859</td>
<td>2.245 (1.367–3.687)</td>
<td>0.011</td>
<td>0.010</td>
<td>0.021</td>
</tr>
<tr>
<td>Non-O type</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.046</td>
<td>0.001</td>
<td>1.825 (1.791–4.193)</td>
<td>0.003</td>
<td>2.001</td>
<td>0.917</td>
<td>0.317–0.917</td>
<td>0.023</td>
<td>0.859</td>
<td>2.245 (1.367–3.687)</td>
<td>0.011</td>
<td>0.010</td>
<td>0.021</td>
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NRL, neutrophil to lymphocyte ratio; CRP, C-reactive protein; HR, Hazard ratio; CI, confidence interval

Figure 1. Recurrence-free survival according to the peripheral blood lymphocyte count. (A) Patients with non-O blood groups (B) patients with the O blood group.

significant positive association between tumor-related factors (tumor size, tumor stage, and nuclear grade) and recurrence in patients with both O and non-O blood groups. However, the association between host-related factors (ECOG-PS, BMI, PBL, NLR, and CRP) and recurrence in univariate analysis differed significantly according to the ABO blood group. An impaired ECOG-PS, decreased BMI, a low PBL count, a high NLR, and an elevated CRP level were significantly associated with recurrence in patients with non-O blood groups but not in patients with the O blood group. The PBL count (hazard ratio, 0.539 per 10³/µL; 95% confidence interval, 0.317–0.917; P = .023) as well as tumor stage and nuclear grade were independent predictors of recurrence in patients with non-O blood groups. In patients with the O blood group, only tumor stage was a predictor of recurrence in multivariate analysis (Table 2). Figure 1 shows RFS curves according to the PBL count. The median PBL count (1700/µL) was used as the cut-off value for dividing patients into low (<1700/µL) and high (≥1700/µL) PBL groups. A low PBL count (<1700/µL) was significantly associated with recurrence in patients with non-O blood types (P = .003) but not in patients with the O blood type (P = .859).
DISCUSSION

The ABO blood group has been known to influence the plasma levels of the von Willebrand factor (VWF)–factor VIII (FVIII) complex, and individuals with O blood type are known to have significantly lower levels of VWF and FVIII than those with non-O blood types (Franchini et al., 2012). Thus, many research groups have investigated association between ABO blood group and the risk of bleeding and thrombotic diseases. Currently, individuals with non-O blood types are thought to have a higher risk of deep vein thrombosis and coronary heart disease than those with the O blood type (Wu O et al 2008, He M et al 2012). With regard to cancer, a number of studies have demonstrated that individuals with non-O blood types have a higher risk of developing various cancers (i.e., gastric and pancreatic cancers) than those with the O blood type (Edgren et al., 2010; Wopin et al., 2009). However, the exact mechanism of this association remains unclear. With regard to prognosis, pancreatic cancer and RCC patients with the O blood type have been reported to have favorable prognosis (Kaffenberger et al., 2012; Rahbani et al., 2012). However, in the present study, we found no statistical difference in RFS between patients with the O blood group and those with non-O blood groups. Thus, further studies are needed to clarify whether RCC patients with the O blood type truly have a favorable prognosis compared to those with non-O blood groups.

Several host-related factors such as BMI, PBL, NLR, and CRP have been reported as important prognostic factors for various cancers (Choi et al., 2012; Sinicropo et al., 2013; Pichler et al., 2013; Saroha et al., 2013; Ghanim et al., 2012) and cardiovascular diseases (Romero-Corral et al., 2006; Gibson et al., 2010; Lomivorotov et al., 2011; Lim et al., 2013). In the present study, impaired ECOG-PS, decreased BMI, a low PBL count, a high NLR, and an elevated CRP level were significantly associated with recurrence in patients with non-O blood groups but not in patients with the O blood group. Therefore, the prognostic value of these host-related factors may differ between patients with non-O and O blood types for various cancers and cardiovascular diseases. Our novel findings that the prognostic relevance of several host-related factors vary according to the blood group in RCC patients could contribute considerably to the design of future studies on prognostic factors for both malignant and non-malignant diseases.

Recent advances in molecular biology have made it possible to obtain a large amount of genetic information on malignant and non-malignant diseases. On the basis of this information, several basic and clinical research studies have been conducted with the intent to develop new therapeutic agents and biomarkers. Some of ultimate goals of biomarker research studies are patient stratification for optimal disease screening according to individual risk, optimal administration of therapeutic agents with minimal adverse effects, and establishment of individualized follow-up protocols, which contribute to personalized medicine. In addition, appropriate patient selection for facilitating efficient clinical trials is another purpose of biomarker research as this may contribute to reduced medical costs. A combination of biomarkers would allow patients to be divided into several small subgroups that consist of individuals with similar disease risk or prognosis profiles. Repetitive patient stratification according to several biomarkers would finally provide each patient with personalized medicine. Thus, it is important to assess the clinical value of biomarkers precisely and accurately. Our results suggest that we should take basic criteria, which are used to stratify individuals (i.e., sex, race, and ABO blood type), into account when we perform biomarker research or clinical trials in the future.

This study is limited by its retrospective design and the analysis of data collected from a single Japanese institution. Further studies considering the effect of racial differences are needed to clarify the association between the ABO blood group and the prognostic value of host-related factors not only in RCC but also in other disease conditions. Nevertheless, we believe the present study provides important insights into the study of prognostic factors in patients with RCC.

CONCLUSIONS

The prognostic value of host-related factors (BMI, PBL, NLR, and CRP), but not tumor-related factors, on RCC recurrence might vary according to the ABO blood group.

REFERENCES


