Malignancy-related ascites in palliative care units: prognostic factor analysis

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ABSTRACT

Objectives The prognostic factors in patients with malignancy-related ascites (MA) have been poorly investigated. This study aimed to evaluate both the prognostic impact of MA on terminally ill patients with cancer and the prognostic factors in those with MA.

Methods This was a post hoc analysis of a multicentre, prospective cohort study. Patients with advanced cancer admitted to palliative care units at 23 institutions and aged ≥18 years were enrolled between January and December 2017. Overall survival (OS) was compared according to MA. A multivariate analysis was conducted to explore prognostic factors in patients with MA.

Results Of 1896 eligible patients, gastrointestinal and hepatobiliary pancreatic cancers accounted for 42.5%. 568 (30.0%) of the total had MA. Patients with MA had significantly shorter OS than those without MA (median, 14 vs 22 days, respectively; HR, 1.55; 95% CI, 1.39 to 1.72; p<0.01). A multivariate analysis showed that MA was a poor prognostic factor (HR, 1.30; 95% CI, 1.13 to 1.50; p<0.01) and that among patients with MA, significant poor prognostic factors were liver metastasis, moderately to severely reduced oral intake, delirium, oedema, gastric cancer, high serum creatinine, high serum C reactive protein, high serum total bilirubin, dyspnnoea and fatigue, while significant good prognostic factors were female sex, good performance status, high serum albumin and colorectal cancer.

Conclusions MA had a negative impact on survival in terminally ill patients with cancer. A multivariate analysis revealed several prognostic factors in patients with terminal cancer and MA.

INTRODUCTION

Malignancy-related ascites (MA) accounts for about 10% of all ascites cases. MA is usually caused by peritoneal carcinomatosis and less commonly by portal hypertension due to massive liver metastases, liver cirrhosis with hepatocellular carcinoma and chylous ascites with malignant lymphoma. MA often occurs in the end stage of gastrointestinal and ovarian cancers and causes various symptoms such as abdominal swelling and pain, nausea, anorexia, vomiting and dyspnnoea. The median survival time after MA diagnosis ranges from 1 to 4 months. While MA is associated with a poor prognosis and deterioration in quality of life, the prognostic factors in patients with MA have been poorly investigated. No prospective studies have explored this issue. A retrospective study showed that liver metastasis and low serum albumin (Alb) level were poor prognostic factors in patients with MA, while ovarian cancer was a good prognostic factor. Moreover, the presence of oedema and foregut adenocarcinoma was identified as poor prognostic factors in other studies. The afore-mentioned studies included patients who could receive chemotherapy, and patients with ovarian cancer with MA...
were considered to have longer survival than those with other cancers because ovarian cancers respond well to chemotherapy. Prognostic factor analyses of patients with MA who can be treated with chemotherapy are influenced by the sensitivity of the primary tumour to chemotherapy and newly developed drugs. Although it is preferable to account for the influence of chemotherapy in cross-organ prognostic factor analysis, no studies have explored prognostic factors in patients with MA who do not receive chemotherapy. The accurate prediction of prognosis can help support patient decision-making and improve the quality of patient care at the end of life. Patients organise their affairs and plan special events or meetings based on their prognosis. Patients with terminal cancer also benefit from reducing overtreatment and undertreatment. Common palliative treatments for MA in Japan have reduced hydration, paracentesis and the use of analgesics, although there is no established evidence for these. Paracentesis can be too invasive for frail patients in palliative care units (PCUs) (ie, inpatient hospices) due to adverse events such as hypotension, renal damage, visceral injury and infection. The implantation of a peritoneal catheter is considered for patients requiring repeated paracentesis. Although this reduces the need for repeat punctures, it can cause adverse events such as cellulitis and peritonitis, and costs more than paracentesis. Additionally, a percutaneous peritoneovenous (Denver) shunt is an optional treatment for patients with MA; however, there is a risk of severe adverse events, including infection, disseminated intravascular coagulation and volume overload. Therefore, palliative treatments for MA should be determined by the extent of tumour invasion and the patient’s status and prognosis.

To predict end-of-life prognosis, the Palliative Prognostic Index (PPI) and Palliative Prognostic Score (PaP Score) are commonly used. The PPI consists of the following factors: Palliative Performance Scale Score, oral intake, oedema, dyspnoea at rest and delirium. On the other hand, the PaP Score comprises dyspnoea, anorexia, Karnofsky Performance Status (KPS), the clinical prediction of survival, white blood cell count and lymphocyte percentage. The sensitivity and specificity of 21-day survival for these scales range from 69.9% to 75% for the PPI and from 83.7% to 84% for PaP Score. These scales include symptoms caused by MA but not the presence of MA. It is unknown whether the presence of MA negatively impacts survival in terminally ill patients with cancer, even when adjusted for the factors included in these scales. In addition, these scales are not specific to patients with MA. Therefore, it is necessary to explore prognostic factors in patients with terminally ill cancer and MA to accurately predict prognosis.

This study was performed to evaluate the prognostic impact of MA on terminally ill patients with cancer and to investigate prognostic factors in this population.

**METHODS**

**Design**

This study was a post hoc analysis of the East-Asian Collaborative Cross-Cultural Study to Elucidate the Dying Process (EASED), an international, multicentre, prospective cohort study that clarified the dying process and end-of-life care in patients with advanced cancer admitted to PCUs in Japan, South Korea and Taiwan. The data from 23 Japanese PCUs were used in this analysis.

Patients from 23 institutions were enrolled in the EASED study from January to December 2017. Key eligibility criteria were age ≥18 years, diagnosis of advanced cancer and first-time admission to a PCU. Eligible patients were followed up until death, 6 months after study enrolment or PCU discharge. Patients scheduled to be discharged within a week and those for whom participation was refused either by the patient or their family were excluded. This study was conducted in accordance with the ethical guidelines for medical and health research involving human subjects presented by the Ministry of Health, Labour and Welfare of Japan.
Measurements

The following data were collected on admission: sex, age, liver metastasis, degree of oral intake, delirium, KPS, oedema, primary cancer site and presence of ascites. The presence of ascites was determined by physical assessment or imaging scans (eg, X-ray, CT or ultrasound) performed in a previous hospital. Patients with ascites were defined as the MA group. The degree of oral intake was classified as ‘normal’, ‘moderately reduced’ (reduced but more than mouthfuls) or ‘severely reduced’ (mouthfuls or less). If blood tests were performed from 1 week before admission to 3 days afterward, the following data were collected: serum Alb, serum creatinine (Cr), serum C reactive protein (CRP) and serum total bilirubin (T-Bil). Physicians graded dyspnoea, pain and fatigue on admission using the Integrated Palliative Care Outcome Scale (IPOS). Each item was classified from 0 (best) to 4 (worst).

Statistical analysis

The primary outcome was overall survival (OS). OS was defined as the time from PCU admission to death or was censored if patients were discharged alive. Patients were divided according to the presence or absence of MA, and OS was compared between the two groups using the Kaplan-Meier method and the log-rank test. Subgroup analysis was performed to identify patients in whom OS was particularly impacted by MA. To assess the prognostic impact of primary cancer, OS according to primary cancer site in patients with MA was compared using the Kaplan-Meier method and the log-rank test. In addition, prognostic factors for OS were explored as secondary outcomes using

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of all patients and patients with or without malignancy-related ascites (MA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients, n (%)</td>
</tr>
<tr>
<td>Total number</td>
<td>1896</td>
</tr>
<tr>
<td>Age (median (IQR))</td>
<td>74 (65–81)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>931 (49.1)</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>730 (38.5)</td>
</tr>
<tr>
<td>Oral intake</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>341 (18.0)</td>
</tr>
<tr>
<td>Moderately reduced</td>
<td>987 (52.1)</td>
</tr>
<tr>
<td>Severely reduced</td>
<td>566 (29.9)</td>
</tr>
<tr>
<td>Delirium</td>
<td>428 (22.6)</td>
</tr>
<tr>
<td>KPS (median (IQR))</td>
<td>40 (30–50)</td>
</tr>
<tr>
<td>Oedema</td>
<td>871 (45.9)</td>
</tr>
<tr>
<td>Primary cancer site</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>203 (10.7)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>240 (12.7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>202 (10.7)</td>
</tr>
<tr>
<td>Ovary</td>
<td>49 (2.6)</td>
</tr>
<tr>
<td>Others</td>
<td>1202 (63.4)</td>
</tr>
<tr>
<td>Alb g/dL (median (IQR))</td>
<td>2.4 (2.0–2.9)</td>
</tr>
<tr>
<td>Cr mg/dL (median (IQR))</td>
<td>0.73 (0.53–1.09)</td>
</tr>
<tr>
<td>CRP mg/dL (median (IQR))</td>
<td>5.2 (2.0–11.0)</td>
</tr>
<tr>
<td>T-Bil mg/dL (median (IQR))</td>
<td>0.6 (0.4–1.2)</td>
</tr>
<tr>
<td>Dyspnoea, IPOS</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>1416 (74.7)</td>
</tr>
<tr>
<td>2–4</td>
<td>380 (20.0)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>100 (5.3)</td>
</tr>
<tr>
<td>Pain, IPOS</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>1132 (59.7)</td>
</tr>
<tr>
<td>2–4</td>
<td>664 (35.0)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>100 (5.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>997 (52.6)</td>
</tr>
<tr>
<td>2–4</td>
<td>787 (41.5)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>112 (5.9)</td>
</tr>
</tbody>
</table>

Alb, albumin; Cr, serum creatinine; CRP, serum C reactive protein; IPOS, Integrated Palliative Care Outcome Scale; KPS, Karnofsky Performance Status; MA, malignancy-related ascites; T-Bil, serum total bilirubin.
a multivariate analysis with Cox regression models. Factors included in subgroup analysis and multivariate analysis were the presence or absence of MA, sex, age (median), liver metastasis, degree of oral intake (normal, moderately reduced or severely reduced), delirium, KPS (<40 or ≥40), oedema, primary cancer site (gastric, colorectum, pancreas, ovary, others), Alb (median), Cr (<1.5 or ≥1.5), CRP (median), T-Bil (<4.0 or ≥4.0) and IPOS scores for dyspnoea, pain and fatigue (0–1 or 2–4). Cut-offs for liver and kidney dysfunction were defined in a previous study on ascites. Patients with missing values were excluded from the multivariate analysis.

Baseline patient characteristics were compared using the t-test, Mann-Whitney U test, $\chi^2$ test or Fisher’s exact test, as appropriate. A two-tailed $p$ value of <0.05 was considered significant. All analyses were conducted using EZR V1.55.
RESULTS

Patient characteristics

Of 1971 eligible patients, 75 were excluded because they were scheduled to be discharged within a week (n=42), were lost to follow-up (n=30) or they or their family refused participation (n=3). Finally, we analysed 1896 patients consisting of 1328 patients without MA (70.0%) and 568 patients with MA (30.0%) at the time of admission (figure 1).

The baseline characteristics of all patients and those with or without MA are shown in table 1. Gastrointestinal cancer accounted for 443 patients (23.4%), pancreatic cancer for 202 patients (10.7%) and hepatobiliary cancer for 161 patients (8.5%). Overall, gastrointestinal and hepatobiliary pancreatic cancers accounted for 42.5% of the total number of patients. Compared with patients without MA, those with MA were younger; more likely to be female, to have liver metastasis and to have oedema; and had reduced oral intake, lower Alb, worse liver and renal function, better IPOS dyspnoea score and worse IPOS fatigue score. In addition, gastrointestinal and ovarian cancers were more common in patients with MA than in those without.

Survival

Patients with MA had significantly shorter OS than those without MA (median, 14 vs 22 days, respectively; HR, 1.55; 95% CI, 1.39 to 1.72; p<0.001) (figure 2).

In subgroup analysis, MA negatively impacted OS in all subgroups except that with ovarian cancer and that with an IPOS dyspnoea score of 2–4 (figure 3).

In patients with MA, OS did not differ between primary cancer sites (median OS, 15 days (95% CI, 13 to 21) for stomach, 16 days (95% CI, 14 to 20) for colorectum, 15 days (95% CI, 10 to 18) for pancreas and 14 days (95% CI, 11 to 24) for ovary; p=0.205) (figure 4).

Prognostic factors

A total of 476 patients were excluded from the multivariate analysis due to missing values. A multivariate analysis in 1420 patients showed that MA was a poor prognostic factor (HR, 1.30; 95% CI, 1.13 to 1.50; p<0.01) (table 2). Additionally, a multivariate analysis to explore prognostic factors in patients with MA showed that liver metastasis (HR, 1.48; 95% CI, 1.30 to 1.68; p<0.01), moderately reduced oral intake (HR, 1.35; 95% CI, 1.14 to 1.59; p<0.01), severely reduced oral intake (HR, 2.02; 95% CI, 1.67 to 2.44; p<0.01), delirium (HR, 1.33; 95% CI, 1.15 to 1.54; p<0.01), oedema (HR, 1.28; 95% CI, 1.14 to 1.45; p<0.01), gastric cancer (HR, 1.36; 95% CI, 1.13 to 1.64; p<0.01), Cr ≥1.5 (HR, 1.45; 95% CI, 1.22 to 1.72; p<0.01), CRP ≥5.2 (HR, 1.35; 95% CI, 1.20 to 1.53; p<0.01), T-Bil ≥4.0 (HR, 1.48; 95% CI, 1.22 to 1.81; p<0.01), IPOS dyspnoea scores of 2–4 (HR, 1.74;
95% CI, 1.51 to 2.01; \( p < 0.01 \)) and IPOS fatigue scores of 2–4 (HR, 1.21; 95% CI, 1.07 to 1.36; \( p < 0.01 \)) were significant poor prognostic factors in patients with MA. On the other hand, female sex (HR, 0.86; 95% CI, 0.76 to 0.97; \( p = 0.01 \)), KPS≥40 (HR, 0.63; 95% CI, 0.55 to 0.73; \( p < 0.01 \)), Alb≥2.4 (HR, 0.84; 95% CI, 0.74 to 0.96; \( p < 0.01 \)) and colorectal cancer (HR, 0.82; 95% CI, 0.69 to 0.98; \( p = 0.03 \)) were significant good prognostic factors (table 3). Ovarian cancer was not associated with prognosis in patients with MA.

**DISCUSSION**

This study revealed that MA negatively impacted survival in terminally ill patients with cancer. In patients with MA, survival time did not differ between primary cancer sites. A multivariate analysis revealed that liver metastasis, reduced oral intake, delirium, oedema, gastric cancer, liver and renal dysfunction, high-inflammation status and severity of dyspnoea and fatigue were significant poor prognostic factors in patients with MA. On the other hand, female sex, high KPS, high Alb and colorectal cancer were identified as significant good prognostic factors in those with MA.

Patients in our study had been admitted to PCUs and could not receive aggressive treatments such as chemotherapy or radiotherapy. Therefore, our study evaluated the natural history of MA in the last few weeks of life. A total of 1896 patients were enrolled from various institutions, and a large amount of prospective data was collected. This study is important for clinicians and patient families because it provides valuable information on the natural history of MA and its impact on survival.
data was collected. Patients with MA accounted for 30.0% of all patients, which was more than previously reported. First, because this study included patients in the PCUs, cancer status is considered to be more progressive. Second, 42.5% of the total patients had gastrointestinal, hepatobiliary or pancreatic cancer. Third, the low Alb levels of the patients at baseline may have influenced the increase in ascites. The median OS was 8 days shorter in patients with MA than in those without MA. A multivariate analysis was performed because of the different backgrounds of patients with and without MA, and MA was shown to be a significant poor prognostic factor. Additionally, we explored prognostic factors in patients with MA and evaluated whether various primary cancer sites or symptoms that were probably due to MA were prognostic factors in this population. The multivariate analysis revealed that liver metastasis, moderately reduced oral intake, severely reduced oral intake, delirium, oedema, gastric cancer, Cr ≥ 1.5, CRP ≥ 5.2, T-Bil ≥ 4.0, IPOS dyspnoea scores of 2–4 and IPOS fatigue scores of 2–4 were significant poor prognostic factors in patients with MA, while female sex, KPS ≥ 40, Alb ≥ 2.4 and colorectal cancer were significant good prognostic factors. Retrospective studies in patients with MA identified liver metastasis, high serum bilirubin level and low Alb level as poor prognostic factors and ovarian cancer as a good prognostic factor. In addition, the degree of oral intake, delirium, oedema, performance status, Alb, CRP, dyspnoea and fatigue are well-known prognostic factors in terminally ill patients with cancer and they are included in various prognostic scores. In contrast to previous reports, this study found that patients with MA who had ovarian cancer exhibited similar OS as patients with other cancers, and a multivariate analysis showed that ovarian cancer was not a prognostic factor. This suggests that ovarian cancer in patients with MA may have a favourable prognosis due to its good sensitivity to chemotherapy, and in the absence of chemotherapy, its prognosis is no different from those of other cancers.

This study had several strengths. First, it was a post hoc analysis of a large, multicentre, prospective cohort study in patients with advanced cancer admitted to PCUs in Japan. Previous studies were retrospective and included a small number of patients. Therefore, this study has high generalisability. Second, this is the first study to evaluate the prognostic impact of MA in end-stage patients and prognostic factors in patients with MA. Third, there were few censored cases because almost all patients were followed up until their death. Fourth, many parameters were collected on admission to PCUs.

On the other hand, this study had several limitations. First, we did not evaluate the amount of ascites. Compared with mild ascites, severe ascites is associated with worse pain and dyspnoea and more decreased appetite. Patients in our study did not necessarily undergo imaging scans when they were administered to PCUs, and the presence of ascites was analysed by physical examination or images taken in a previous hospital. Therefore, data on the amount of ascites were not available. The diagnosis of ascites on CT scan may include many patients with asymptomatic ascites. In fact, paracentesis was performed in 15.0% of patients with MA. Colorectal cancer was identified as a favourable prognostic factor in the multivariate analysis, but this may be because the analysis did not include the amount of ascites as a covariate. Second, the cause and characteristics of ascites were unknown in this study, and these factors may be related to prognosis. We defined the presence of ascites as MA because symptom control is prioritised over determining the cause and characteristics of ascites in PCUs. Ascites in patients with cancer is not necessarily caused by peritoneal carcinomatosis. Further studies are needed to assess whether survival depends on ascites characteristics. Third, this study did not attempt to identify patients whose MA appeared after admission to PCUs. Fourth, the symptoms evaluated in this study (dyspnoea, pain and fatigue) may not always have been related to MA. Factors other than MA may have affected the prognosis. Fifth, this study did not include patients who received care at home or in acute care hospitals. Therefore, care should be taken when applying our results to these patients. Sixth, not all patients received blood tests from 1 week before admission to 3 days afterward. Missing values might have affected the results. Considering these strengths and limitations, the results of this study are valuable given that this was a prospective, large-scale study. Prognostic factors identified in this study should be considered when treating MA.

In conclusion, MA had a negative impact on survival in terminally ill patients with cancer. A multivariate analysis revealed several known prognostic factors in patients with terminal cancer and MA.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants. The EASED study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the ethical guidelines for epidemiological research presented by the Ministry of Health, Labour and Welfare in Japan. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon request.

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