Association of protein-energy wasting and inflammation status with mortality after coronary revascularisation in patients on haemodialysis

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INTRODUCTION

Over the past decade, cardiorenal interactions have been featured because patients with chronic kidney disease (CKD) frequently experience cardiovascular disease (CVD) and vice versa.1 Particularly in subjects requiring haemodialysis (HD), coronary artery disease (CAD) reportedly presents in over half of patients, even at the beginning of HD therapy,2 and is the leading cause of death in this population.3 In such situations, coronary revascularisation with coronary artery bypass graft surgery (CABG)4–6 or percutaneous coronary intervention (PCI) is performed in HD patients worldwide. However, their prognosis is still markedly poorer compared with that of the general population.4–6 On the other hand, protein-energy wasting (PEW),9 a state of decreased body protein mass and energy fuel, is reportedly prevalent in CKD patients9,10 and consistently associated with increased risks of cardiovascular mortality.12 PEW can result not only from an inadequate diet but also be induced by inflammatory processes.9,13,14 Moreover, inflammatory status itself is associated with mortality in this population.15 In these contexts, we investigated the association of the geriatric nutritional risk index (GNRI)16 as a surrogate marker of the PEW, C reactive protein (CRP) and their combined predictive value for CVD.
and all-cause mortality after coronary revascularisation in chronic HD patients.

METHODS

Patients
From April 2001 to December 2011, a total of 721 HD patients electively underwent coronary revascularisation and were enrolled in this study. In advance, patients with acute myocardial infarction, those hospitalised due to other active diseases and those with a history of malignancies were excluded. Diabetes, hypertension and dyslipidaemia were defined according to each guideline. Multivessel disease was defined as the presence of a lesion at more than two vessels among the right coronary artery, left anterior descending artery and left circumflex artery and/or left main trunk disease. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson’s method via ultrasonic echocardiography. In patients undergoing CABG, the off-pump technique was selected, and the internal thoracic arteries were used if possible. In patients treated with PCI, drug-eluting stent (DES) was used if the patients had no contraindications.

The GNRI and CRP measurements
Blood samples to determine serum albumin and CRP levels were taken at the just preperiod of procedural day. The GNRI was calculated from the individually obtained serum albumin levels and body weight as follows, reported by Yamada et al.20

\[
\text{GNRI} = [14.89 \times \text{albumin (g/dl)}] + [41.7 \times (\text{body weight/ideal body weight})]
\]

The body weight/ideal body weight was set to 1 when a patient’s body weight exceeded the ideal body weight. Ideal body weight was defined as the value calculated from height and a body mass index (BMI) of 22 kg/m².20 All patients underwent HD therapy before 1 day prior procedural day, and body weight after HD therapy was used to calculate the GNRI. The serum CRP was measured using latex-enhanced highly sensitive CRP immunoassay. Thereafter, patients were divided into tertiles according to their GNRI and CRP levels.

Follow-up study
The follow-up was concluded in December 2012. The primary endpoint was CVD-cause death, including that due to heart failure, myocardial infarction, arrhythmia, sudden death, stroke, peripheral artery disease (PAD) and other CVD-related death. The data for the endpoints were obtained from hospital charts and through telephone interviews with patients conducted by trained reviewers who were blinded to the protocol. In the present study, cases of unwitnessed death were counted as cardiac death. Second endpoint was all-cause death.

Statistical analyses
Variables with a normal distribution were expressed as mean ±SD, and asymmetrically distributed data were given as the median and IQR. Differences between the groups were evaluated by the one-way analysis of variance or Kruskal-Wallis test for continuous variables and by the \(X^2\) test for categorical variables. Differences in event-free survival among the groups were examined with the Kaplan-Meier method and compared using a log-rank test. HRs (HR) and 95% CIs were calculated for each factor via a Cox proportional hazards analysis. All baseline variables with \(p<0.05\) by univariate analysis were entered into a multivariate model to determine the independent predictors for the endpoint. To assess whether the predictability for mortality would improve after the addition of the GNRI, CRP and/or both of them into a baseline model with established risk factors, we calculated the C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The C-index is defined as the area under receiver-operating characteristic curves between individual predictive probabilities for mortality and the incidence of mortality and was compared among each predicting model.21 The NRI relatively indicates how many patients improve their predicted probabilities for mortality, while the IDI represents the average improvement in predicted probabilities for mortality after adding variables into the baseline model.22 Differences were considered statistically significant at \(p<0.05\). The statistical analyses were performed using the SAS V.6.10 software (SAS Institute).

Patient and public involvement
Patients and public were not involved in this study.

RESULTS
Of the enrolled patients, 592 patients underwent PCI and 129 patients underwent CABG based on the decision made primarily by the patients after adequate explanation by their physicians. The patients were divided into tertiles according to their GNRI levels (tertile 1 (T1):<91.5, T2: 91.5–98.1, and T3:>98.1) and CRP levels (T1:<1.4 mg/L, T2: 1.5–7.0 mg/L, and T3:>7.1 mg/\(\text{al}\)). The clinical characteristics of the patients are shown in table 1. The median of the CRP levels were 5.8 (1.1–18.3) mg/L, 3.0 (1.0–9.0) mg/L, and 2.1 (1.0–8.0) mg/L in T1, T2 and T3 of the GNRI, respectively (\(p=0.0001\)). Inversely, the GNRI levels were 95.9±7.6, 95.0±8.3, and 92.6±9.8 in T1, T2 and T3 of the CRP, respectively (\(p=0.0001\)).

During the follow-up period (median: 53 months), 222 cases experienced death (30.8%), including 125 cases of CV death (17.3%). Also, four patients underwent renal transplantation, and were censored at the point of moving out. The Kaplan-Meier analysis showed that the 10-year survival rate was 32.3%, 44.8% and 72.5% in T1, T2 and T3 of the GNRI and 60.9%, 49.2% and 23.5% in T1, T2 and T3 of the CRP, respectively (\(p<0.0001\) in both) (figure 1). For CVD-cause mortality, similar results were obtained (55.8%, 62.7% and 80.3%, \(p=0.0001\), and 76.2%, 66.2%, and 38.7%, \(p=0.0001\), respectively) (figure 2). After adjusting for age, multivessel disease,
### Table 1  Clinical characteristics

|                        | All patients (n=721) | GNRI |                       |                       |                       | P value |
|------------------------|----------------------|------|-----------------------|-----------------------|-----------------------|---------|
|                        |                      | <91.5 (n=240) | 91.5–98.1 (n=242) | >98.1 (n=239) |                       |         |
| Male gender (%)        | 71.7                 | 68.3  | 67.8                  | 79.1                  | 0.087                 |         |
| Age (years)            | 66±10                | 69±9  | 66±9                  | 64±10                 | <0.0001               |         |
| Duration of HD (years) | 3.8 (1.2–10.4)       | 6.1 (1.2–11.6) | 3.9 (1.6–9.4) | 2.8 (0.5–6.5) | 0.036                 |         |
| Diabetes (%)           | 57.7                 | 56.7  | 58.3                  | 58.2                  | 0.93                  |         |
| Hypertension (%)       | 59.8                 | 66.3  | 59.1                  | 54.0                  | 0.023                 |         |
| Dyslipidaemia (%)      | 28.7                 | 25.4  | 28.9                  | 32.6                  | 0.25                  |         |
| Smoking (%)            | 29.6                 | 28.0  | 28.9                  | 31.8                  | 0.73                  |         |
| Body mass index (kg/m²)| 21.4±3.3             | 18.7±2.2 | 21.5±2.2 | 24.2±2.8 | <0.0001               |         |
| PAD (%)                | 38.7                 | 38.3  | 39.7                  | 38.1                  | 0.93                  |         |
| Stroke (%)             | 19.0                 | 21.9  | 17.9                  | 17.2                  | 0.37                  |         |
| GNRI                   | 94.5±8.7             | 85.1±5.3 | 94.7±1.9  | 103.8±4.8 | <0.0001               |         |
| Haemoglobin (g/dL)     | 10.6±1.3             | 10.4±1.4 | 10.6±1.3 | 10.7±1.2 | 0.12                  |         |
| Albumin (g/dL)         | 3.6±0.4              | 3.3±0.3 | 3.6±0.2  | 3.9±0.3   | <0.0001               |         |
| Total cholesterol (mg/dL) | 168±35             | 169±38 | 167±34    | 167±35    | 0.83                  |         |
| LDL-cholesterol (mg/dL) | 99±28               | 98±29  | 96±25     | 96±30     | 0.81                  |         |
| HDL-cholesterol (mg/dL) | 44±13              | 45±12  | 44±13     | 42±13     | 0.077                 |         |
| CRP (mg/l)             | 3.0 (1.0–10.9)       | 5.8 (1.1–18.3) | 3.0 (1.0–9.0) | 2.1 (1.0–8.0) | 0.0001               |         |
| LVEF                   | 0.59±0.14            | 0.56±0.16 | 0.61±0.13 | 0.60±0.13 | 0.0020                |         |
| Procedure (%)          |                      |       |                       |                       | 0.069                 |         |
| CABG                   | 17.9                 | 21.3  | 19.0                  | 13.4                  |                       |         |
| PCI                    | 82.1                 | 78.7  | 81.0                  | 86.6                  |                       |         |
| Multivessel disease (%)| 57.6                 | 60.8  | 55.8                  | 56.1                  | 0.45                  |         |
| LMT disease (%)        | 6.1                  | 6.7   | 5.4                   | 6.3                   | 0.83                  |         |
| LAD disease (%)        | 74.1                 | 73.5  | 75.4                  | 73.2                  | 0.84                  |         |
| Statins (%)            | 14.0                 | 12.9  | 11.9                  | 17.8                  | 0.19                  |         |
| β-blocker (%)          | 26.3                 | 23.3  | 24.3                  | 31.8                  | 0.12                  |         |
| ARB/ACEI (%)           | 43.7                 | 42.9  | 44.0                  | 44.3                  | 0.95                  |         |
| Calcium antagonist (%) | 41.3                 | 41.9  | 41.7                  | 40.0                  | 0.91                  |         |

### Serum CRP

| Serum CRP | ≤1.4 mg/L (n=241) | 1.5–7.0 mg/L (n=241) | ≥7.1 mg/L (n=239) | P value |
|-----------|-------------------|----------------------|-------------------|---------|
| Male gender (%) | 68.9               | 72.8                 | 71.7              | 0.48    |
| Age (years) | 65±9               | 66±10                | 68±10             | 0.010   |
| Duration of HD (years) | 4.4 (0.8–11.8) | 3.6 (1.3–11.6) | 3.5 (1.3–10.2) | 0.98    |
| Diabetes (%) | 58.9               | 52.7                 | 61.5              | 0.13    |
| Hypertension (%) | 58.1               | 60.6                 | 60.7              | 0.81    |
| Dyslipidaemia (%) | 25.3               | 29.5                 | 33.1              | 0.20    |
| Smoking (%) | 29.5               | 30.7                 | 27.8              | 0.85    |
| Body mass index (kg/m²) | 21.4±2.9            | 21.6±3.3       | 21.5±3.5          | 0.77    |
| PAD (%) | 34.4               | 37.8                 | 43.9              | 0.096   |
| Stroke (%) | 17.2               | 20.5                 | 19.3              | 0.64    |
| GNRI | 95.9±7.6            | 95.0±8.3             | 92.6±9.8          | <0.0001 |
| Haemoglobin (g/dL) | 10.8±1.2            | 10.6±1.3             | 10.4±1.4          | 0.14    |

Continued
Table 1 Continued

| Serum CRP | ≤1.4 mg/L (n=241) | 1.5–7.0 mg/L (n=241) | ≥7.1 mg/L (n=239) | P value |
|-----------|-------------------|---------------------|-------------------|---------|
| Albumin (g/dL) | 3.7±0.3 | 3.6±0.3 | 3.5±0.2 | <0.0001 |
| Total cholesterol (mg/dL) | 166±35 | 167±30 | 171±33 | 0.53 |
| LDL-cholesterol (mg/dL) | 93±26 | 96±28 | 104±33 | 0.013 |
| HDL-cholesterol (mg/dL) | 47±14 | 43±12 | 42±11 | 0.0026 |
| CRP (mg/l) | 1.0 (0.8–1.1) | 3.0 (2.0–5.0) | 19.0 (11.0–43.0) | <0.0001 |
| LVEF | 0.62±0.12 | 0.58±0.14 | 0.58±0.15 | 0.018 |
| Procedure (%) | | | | 0.15 |
| CABG | 16.7 | 15.3 | 21.8 | |
| PCI | 83.3 | 84.7 | 78.2 | |
| Multivessel disease (%) | 53.9 | 57.3 | 61.5 | 0.24 |
| LMT disease (%) | 5.4 | 7.5 | 5.4 | 0.56 |
| LAD disease (%) | 77.4 | 68.3 | 76.5 | 0.074 |
| Statins (%) | 12.1 | 12.9 | 16.9 | 0.32 |
| β-blocker (%) | 31.5 | 23.0 | 24.2 | 0.11 |
| ARB/ACEI (%) | 45.1 | 42.1 | 43.9 | 0.82 |
| 2calcium antagonist (%) | 44.2 | 38.8 | 40.9 | 0.53 |

Bold data are expressed as mean±SD or median (IQR).

ACEI, Angiotensin-converting-enzyme inhibitor; ARB, Angiotensin II Receptor Blocker; CABG, coronary artery bypass grafting; CRP, C reactive protein; GNRI, geriatric nutritional risk index; HD, haemodialysis; HDL, high density lipoprotein; LAD, left anterior descending artery; LDL, low density lipoprotein; LMT, left main trunk; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Figure 1

All-cause survival after coronary intervention among tertiles according to GNRI and CRP levels. CRP, C reactive protein; GNRI, Geriatric Nutritional Risk Index.
Coronary artery disease and LVEF as covariates with p<0.05 by univariate analysis, a declined GNRI (HR 2.40, 95% CI 1.58 to 3.74, p<0.0001 for T1 vs T3) and elevated CRP (HR 2.31, 95% CI 1.58 to 3.43, p<0.0001 for T3 vs T1) were identified as independent predictors of all-cause mortality (Table 2). Similarly, both variables could predict CVD-cause mortality as well.

**Table 2** Predictive value of GNRI and CRP for cardiovascular-cause and all-cause mortality

|                     | Non-adjusted | P value | Adjusted* | P value |
|---------------------|--------------|---------|-----------|---------|
| GNRI (vs T3)        |              |         |           |         |
| T2                  | 1.61 (0.96 to 2.77) | <0.0001 | 1.67 (0.94 to 3.12) | <0.0001 |
| T1                  | 2.95 (1.82 to 3.87) | <0.0001 | 2.45 (1.39 to 4.54) | <0.0015 |
| GNRI (continuous)   | 0.94 (0.92 to 0.96) | <0.0001 | 0.96 (0.94 to 0.98) | <0.0001 |
| CRP (vs T1)         |              |         |           |         |
| T2                  | 1.44 (0.89 to 2.37) | 0.13    | 1.58 (0.89 to 2.84) | 0.11    |
| T3                  | 2.56 (1.63 to 4.11) | <0.0001 | 2.98 (1.77 to 5.22) | <0.0001 |
| Log CRP             | 2.09 (1.57 to 2.77) | <0.0001 | 1.83 (1.37 to 2.43) | <0.0001 |

**All-cause mortality**

|                     | Non-adjusted | P value | Adjusted* | P value |
|---------------------|--------------|---------|-----------|---------|
| GNRI (vs T3)        |              |         |           |         |
| T2                  | 1.58 (1.07 to 2.36) | 0.019   | 1.54 (1.01 to 2.42) | 0.048   |
| T1                  | 2.99 (2.09 to 4.39) | <0.0001 | 2.40 (1.58 to 3.74) | <0.0001 |
| GNRI (continuous)   | 0.95 (0.93 to 0.96) | <0.0001 | 0.96 (0.94 to 0.98) | <0.0001 |
| CRP (vs T1)         |              |         |           |         |
| T2                  | 1.53 (1.07 to 2.20) | 0.018   | 1.39 (0.93 to 2.10) | 0.10    |
| T3                  | 2.46 (1.76 to 3.49) | <0.0001 | 2.31 (1.58 to 3.43) | <0.0001 |
| Log CRP             | 1.89 (1.53 to 2.33) | <0.0001 | 1.68 (1.35 to 2.08) | <0.0001 |

*Adjusted for age, multivessel disease and LVEF as covariates with p<0.05 by univariate analysis.
CRP, C reactive protein; CVD, cardiovascular disease; GNRI, Geriatric Nutritional Risk Index; LVEF, left ventricular ejection fraction.
(HR 2.45, 95% CI 1.39 to 4.54, p=0.0015 for T1 vs T3 of the GNRI and HR 2.98, 95% CI 1.77 to 5.22, p<0.0001 for T3 vs T1 of the CRP). In addition, the GNRI and log CRP as continuous value were also independent predictors of all-cause mortality (HR 0.96, 95% CI 0.94 to 0.98, p<0.0001 and HR 1.68, 95% CI 1.35 to 2.08, p<0.0001) and CVD mortality (HR 0.96, 95% CI 0.94 to 0.98, p<0.0001 and HR 1.83, 95% CI 1.37 to 2.43, p<0.0001), respectively (table 2). In addition, when diabetes, hypertension, duration of HD and haemoglobin as clinically important factors were added the multivariate Cox model, the GNRI (HR 0.96, 95% CI 0.94 to 0.97, p<0.0001 for CVD mortality and HR 0.96, 95% CI 0.94 to 0.98, p<0.0001 for all-cause mortality) and log CRP (HR 1.81, 95% CI 1.35 to 2.41, p<0.0001 for CVD mortality and HR 1.70, 95% CI 1.34 to 2.11, p<0.0001 for all-cause mortality) were still independent predictors, respectively. In the combined setting of both variables, the risk of mortality was 5.55 times higher (95% CI 2.64 to 13.6, p<0.0001) in the T1 of the GNRI with the T3 of the CRP than in the T3 of the GNRI with the T1 of the CRP (figure 3). Similar results were also obtained for CVD-cause mortality (HR 14.9, 95% CI 5.26 to 247.4, p<0.0001). Furthermore, the addition of both the GNRI and CRP to a prediction model based on established risk factors—including age, multivessel disease and LVEF as covariates with p<0.05 by univariate analysis—improved the C-index (0.648 to 0.724, p<0.0001), NRI (0.539, p<0.0001) and IDI (0.081, 95% CI 0.054 to 0.109, p<0.0001) for all-cause mortality and CVD-cause mortality, respectively (table 3).

### Table 3: Discrimination of each predicting models for cardiovascular-cause and all-cause mortality using C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI)

|                          | CVD-cause mortality | All-cause mortality |
|--------------------------|---------------------|---------------------|
|                          | C-index (95% CI)    | P value | NRI       | P value | IDI       | P value |
| **CVD-cause mortality**  |                     |         |           |         |           |         |
| Established risk*        | 0.630 (0.562 to 0.698) | Reference | Reference | Reference | Reference |
| +GNRI                    | 0.694 (0.635 to 0.754) | 0.0026 | 0.493     | <0.0001 | 0.029     | <0.0001 |
| +CRP                     | 0.678 (0.611 to 0.745) | 0.0053 | 0.364     | 0.0011 | 0.021 | 0.017 |
| +GNRI and CRP            | 0.718 (0.659 to 0.776) | 0.0002 | 0.510     | <0.0001 | 0.056 | <0.0001 |
| **All-cause mortality**  |                     |         |           |         |           |         |
| Established risk*        | 0.648 (0.596 to 0.699) | Reference | Reference | Reference | Reference |
| +GNRI                    | 0.707 (0.660 to 0.754) | 0.0036 | 0.510     | <0.0001 | 0.060 | <0.0001 |
| +CRP                     | 0.687 (0.637 to 0.736) | 0.0018 | 0.360     | <0.0001 | 0.031 | <0.0001 |
| +GNRI and CRP            | 0.724 (0.678 to 0.770) | 0.0002 | 0.539     | <0.0001 | 0.081 | <0.0001 |

*Including age, multivessel disease and LVEF as covariates with p<0.05 by univariate analysis.

CRP, C reactive protein; CVD, cardiovascular disease; GNRI, Geriatric Nutritional Risk Index; LVEF, left ventricular ejection fraction.
p<0.0001) more than each alone (table 3). Similar results were also obtained for CVD mortality (C-index 0.630 to 0.718, p=0.0002, NRI 0.510, p<0.0001 and IDI 0.056, p<0.0001).

**DISCUSSION**

Until now, the consistent poorer outcome after, regardless of percutaneous, even in the modern DES era, or surgical coronary revascularisation, was considered to be due to various reasons such as complex and/or massive calcified coronary lesions, the presence of multivessel disease or an intolerance for procedural invasion due to accelerated systemic atherosclerosis in chronic HD patients. Thus, our results suggest that preprocedural PEW and/or chronic inflammation status should be newly added to such numerous prognostic factors after coronary revascularisation in this high-risk population.

We have reported that both a declined GNRI and elevated CRP are closely associated with abnormalities of the ankle-brachial index (ABI) and that the combination of these variables additively increases CVD-cause and all-cause mortality risks in HD patients. Other studies have also reported that an abnormal ABI reflects not only PAD but also a systemic atherosclerosis such as overall CVD, including coronary or cerebrovascular diseases. Thus, our previous report might manifest so-called malnutrition, inflammation and atherosclerosis syndrome in patients with CKD. In this context, our present findings might be appropriately explained by these previous findings, as HD patients undergoing coronary intervention, regardless of whether it is surgical or percutaneous, are consistently considered to be a highly atherosclerotic group, even among average HD patients.

Moreover, we have already reported that a preprocedural lower BMI and elevated CRP are independently associated with an incidence of lower limb amputation after infrapopliteal bypass surgery in HD patients with critical limb ischemia (HR 0.86, 95% CI 0.76 to 0.97, p=0.014 and HR 1.06, 95% CI 1.01 to 1.11, p=0.014, respectively). However, interestingly, the predictability of both of these variables were not significant in non-HD patients (HR 0.89, 95% CI 0.57 to 1.32, p=0.52, and HR 1.02, 95% CI 0.98 to 1.06, p=0.31, respectively). Referring to these results, preprocedural malnutrition and inflammation status might possibly CKD-specifically affect poorer outcomes after, regardless of coronary or lower extremity intervention, compared with non-HD patients.

In addition, it has been reported that predictability for mortality with the GNRI is broadly comparable with the diagnostic criteria of PEW recommended by the International Society of Renal Nutrition and Metabolism (PEW-ISRNM) (C-index: 0.819 vs 0.820, p=0.82). Although use of the PEW-ISRNM, including measurement of the mid-arm muscle circumference area or daily protein-energy intake, is accurate to assess PEW, it might be troublesome. In contrast, the GNRI value is easily obtained from daily clinical practice. Therefore, the GNRI may be a useful indicator over the PEW-ISRNM to assess malnutrition in HD patients. In this context, physicians should pay more attention to these pre-procedural comorbidities in this high-risk population.

There are several limitations in the present study. First, all the study subjects were Japanese, who reportedly have a better prognosis compared with patients in the United States and Europe. Second, study subjects were included from only two centres. Third, we did not evaluate HD patients without CAD as the control group. Thus, we could not demonstrate more effect of these comorbidities status in patients with CAD compared with those without. Four, we did not consider impact of changes in GNRI and CRP during follow-up period on outcomes. Changes in BMI or albumin is reportedly associated with mortality.

In conclusion, a preprocedural declined GNRI and elevated CRP, which reflect PEW and chronic inflammation status, are closely associated with CVD-cause and all-cause mortality after coronary revascularisation in chronic HD patients. Furthermore, the combination of both variables could not only stratify the risk of mortalities but also improve the predictability when adding on established risk factors, including age, multivessel disease or LVEF.

**CONTRIBUTORSHIP STATEMENT**

Conception and design of the study: YK, HI and HT. Generation, collection, assembly, analysis and/or interpretation of data: YK, SD, RI, NU and HT. Drafting and/or revision of the manuscript: YK, HI and HT. Approval of the final version of the manuscript: YK, HI, HT, SD, RI, NU and TM.

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**PATIENT CONSENT FOR PUBLICATION**

Not required.

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The study protocol and chart reviews used were approved by the institutional ethics of both hospitals and conducted in accordance with the Declaration of Helsinki.

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Data are available on reasonable request.

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