Red blood cell fatty acid levels improve GRACE score prediction of 2-yr mortality in patients with myocardial infarction

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Abstract

Background—Blood omega-3 and omega-6 fatty acid levels have been associated with reduced risk for total mortality in patients with stable coronary heart disease (CHD), but their relationships with mortality in the setting of myocardial infarction (MI) are unknown.

Objective—To determine the association between red blood cell (RBC) fatty acid levels measured at admission and 2-year mortality in MI patients, independent of the GRACE risk score, a traditional mode of risk stratification,

Design—Admission RBC fatty acid levels were measured in patients enrolled in a prospective, 24-center MI registry (TRIUMPH). Two-year mortality was modeled with Cox proportional hazards regression to assess the extent to which the inclusion of fatty acid levels would improve, over and above the GRACE score, risk stratification for 2-year mortality.

Results—RBC fatty acid data were available from 1,144 patients who did not report taking fish oil supplements after discharge. Two RBC fatty acids [eicosapentaenoic acid (EPA n-3) and docosapentaenoic n-6 (DPA)] were univariate predictors of total mortality. The combined fatty acid c-statistic (0.60, p<0.001) improved the c-statistic of the GRACE score alone from 0.747 (p<0.001) to 0.768 (p<0.05 vs. GRACE alone). The net reclassification index improved by 31% (95% CI, 15% to 48%) and the relative incremental discrimination index improved by 19.8% (7.5% to 35.7%).

Conclusion—RBC EPA and DPA n-6 levels improved the prediction of 2-yr mortality over and above the GRACE score in MI patients.

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Introduction

Identifying patients at higher risk for death after myocardial infarction (MI) is a cornerstone of modern cardiovascular care[1]. The GRACE (Global Registry of Acute Coronary Events) score was developed to better risk-stratify patients admitted with an acute coronary syndrome (ACS) and identify those at increased risk for death over the next 6 months[2]. The c-statistic for the GRACE score was originally reported to be 0.75, but the extent to which it applies to longer term mortality or can be improved upon with other risk markers has received relatively little attention.

Several epidemiologic studies have linked higher fish intake, the primary source of the marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with lower risks of sudden cardiac death[3] and death from coronary heart disease (CHD)[4]. Higher blood levels of EPA + DHA are also associated with a lower risk for death from any cause[5]. In addition, two large post-MI randomized trials found that higher intake of fish[6] and fish oil[7] reduced all-cause mortality and improved cardiovascular (CV) prognosis. On the other hand, a recent 1-year German study in post-MI patients found no effect of 840 mg/d of omega-3 fatty acids on CV endpoints[8], and a study using the same dose in dysglycemic patients reached the same conclusion[9].

Heart cell membrane content of omega-3 fatty acids can be estimated by measuring red blood cell (RBC) fatty acid composition[10;11] which has been shown to be a more stable marker of omega-3 status than plasma levels[12]. The primary known determinants of RBC omega-3 levels are EPA+DHA intake, fish oil supplementation, smoking and age with genetic factors explaining about 25% of the variability[13]. In light of the association between marine omega-3 fatty acid status and CV prognosis, and considering the fact that omega-3 tissue content is modifiable by diet or supplementation[14;15], levels of specific fatty acids could be a valuable addition to risk stratification after MI, and could identify patients for novel treatment strategies to improve prognosis. Although a suite of RBC fatty acids (including certain omega-3, omega-6, trans, saturated and monounsaturated species) showed an improved ability to discriminate ACS cases from controls as compared with classic Framingham risk factors,[16] the prognostic value of the RBC fatty acid patterns in patients presenting with an acute MI is unknown. The aim of the present study was to determine the extent to which admission RBC fatty acid levels 1) predicted 2-year mortality rates and 2) improved upon the GRACE score prediction in patients with acute MI.

Methods

Participants

The Translational Research Investigating Underlying disparities in recovery from acute Myocardial infarction Patient Health status (TRIUMPH) study is a prospective MI registry of 24-centers across the United States[17]). Inclusion criteria were age 18 years with biomarker evidence of myocardial injury (positive troponins or elevated creatinine kinase-MB fraction within 24 hours of hospital admission) and supporting evidence of an acute MI (either ischemic symptoms lasting for > 20 minutes or electrocardiographic ST changes). Patients were excluded if they were incarcerated, refused participation, were unable to provide consent, did not speak English or Spanish, were transferred to the participating hospital from another facility more than 24 hours after initial admission, or expired or were discharged prior to being contacted by the investigators.

Patients were enrolled in TRIUMPH from April 11, 2005 to December 31, 2008. Consecutive patients, enrolled between 04/2005 and 10/2007, who consented to supplemental blood work, also had their RBC membrane fatty acid levels measured and

were included in this analysis. The study protocol was approved by the individual Institutional Review Boards of the participating centers and all participants provided written informed consent. Detailed clinical and treatment characteristics were collected by chart abstractions and standardized interviews performed between 24 and 72 hours after acute MI admission. Trained data collectors at each site acquired the requisite data. Vital status was determined by phone interviews and queries of the social security death master file. Disease-specific morbidity or mortality data were not available.

GRACE score

The GRACE risk score was developed in 15,007 and subsequently validated in 7,638 MI patients from 94 hospitals in 14 countries. In developing the score, many variables were considered: age, sex, medical history (8 items), prior medications (9 items), signs and symptoms at admission (7 items), and in-hospital medical treatments, procedures and complications (25 items). Of these, nine entered the final model: age; histories of myocardial infarction and heart failure; admission heart rate, systolic blood pressure, serum creatinine level; elevated initial serum cardiac biomarker level; ST-segment depression on presenting electrocardiogram; and percutaneous coronary intervention performed in hospital[2]. The GRACE risk score has been shown to provide good discrimination of 6-month mortality (c-statistic = 0.75), even with modern cardiac care, and is well-calibrated[18].

Red blood cell membrane fatty acid levels

RBCs were obtained from ethylenediaminetetraacetic acid (EDTA) blood samples after removal of the plasma and buffy coat and stored at −70°C until thawed for analysis. Briefly, an RBC aliquot was heated at 100°C for 10 minutes with methanol containing 14% boron trifluoride. The fatty acid methyl esters thus generated were extracted with hexane and water and were analyzed via gas chromatography using a GC2010 (Shimadzu Corporation, Columbia, MD) equipped with a 30m capillary column (Omegawax 250, Supelco, Bellefonte, PA)[19]. FAs were identified through comparison with a standard fatty acid methyl ester mixture (GLC-727, Nuchek Prep, Elysian, MN). (Note: *trans* fatty acids were not measurable by this method). The coefficient of variations were <6% for all fatty acids of interest.

Other Laboratory Tests

Plasma lipids and lipoproteins were measured by the VAP test (Atherotech, Inc., Birmingham, AL). Troponin T was measured using Roche Elecsys Troponin T Immunoassay and hs-CRP was measured using Roche Tina-quant CRP (Latex) assay. Serum creatinine levels were determined by the Roche serum creatinine Jaffé method using rate-blanking and compensation.

Statistical Methods

Continuous variables are described as mean ± standard deviation (SD) and were compared using Mantel-Haenszel trend tests. Non-normal data are described as median [interquartile range (IQR)] and are compared using the Kruskal-Wallis test. Categorical variables are described as counts and percentages and were compared using the chi-square test, the Fisher exact test, or the Kruskal-Wallis test as appropriate.

RBC fatty acids of interest were chosen on the basis of their association with 2-year mortality after adjusting for the GRACE score. To best determine the functional relationship between 2-year mortality and RBC FAs we used Martingale residuals calculated from the Proportional Hazard model with the Grace Score as the lone predictor. The Martingale residual can be interpreted as the difference between the observed and the expected number

of events under the assumed Cox model across the range of RBC fatty acid levels[20]. We then performed locally-weighted quadratic regression with a smoothing window of 67% predicting the Martingale residual on fatty acids of interest, as suggested by Klein and Moeschberger[20]. Based on these plots we determined whether the fatty acids of interest had an association with risk and whether that risk was best described as a linear, polynomial, or categorical relationship. We then plotted Kaplan-Meier curves based upon RBC fatty acid tertiles (for linear variables) or cutpoint (for non-linear variables) and computed a trend test p-value.

To determine the extent to which the fatty acids provided incremental information beyond the GRACE score, we tested nested proportional hazard models. Model 1 contained the GRACE risk score, and Model 2 contained GRACE plus the fatty acids of interest. To evaluate the potential improvement in the GRACE score prediction, we then followed the recommendations of Hlatky et al[21]. First we computed the independent significance of the fatty acid markers by Hazard Ratios and 95% CI's. We then computed the survival c-statistics[22] and tested them using the methods by Antolini[23]. Next, we computed the Integrated Discrimination Improvement (IDI) on both the absolute and relative scale, along with the continuous Net Reclassification Improvement (NRI), as described by Pencina[24]. Bootstrapping was used to obtain 95% confidence intervals. The IDI combines the increase in mortality probability provided by including the fatty acid marker for those experiencing an event plus the decrease in mortality probability for those not experiencing an event. Similarly, the continuous NRI is the net proportion of subjects getting correctly reclassified relative to the GRACE score alone. Lastly, we graphically inspected and computed calibration measures using deciles of predicted risk according to the approach of D'Agostino[25]. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

Results

A total of 4277 patients were enrolled in TRIUMPH, and the first 1517 had their admission omega-3 fatty acid levels measured. Baseline characteristics of the patients who had their fatty acids levels measured were similar to those who did not. Of the 1517 patients, 21% (n=320) reported commencing omega-3 supplementation after discharge and were removed from the analysis so that the baseline assessment would be a more accurate reflection of their chronic state. This resulted in a final cohort of 1,197 patients. Vital status at 2 years was available for 1,144 of which 135 (11.8%) had died.

GRACE Risk Score and 2-year Mortality

Although originally validated for 6-month survival, in this study the GRACE score was a significant predictor of 2-year mortality with a c-statistic of 0.75 (p<0.001), with a calibration chi square of 12.53 (p=0.13) indicating good calibration. A comparison of all demographic, behavioral, medical and treatment variables according to mortality status at 2 years is presented in Supplementary Table 1.

RBC Fatty Acids and 2-Year Mortality

RBC fatty acid differences between surviving and dead patients are shown in Table 1. Three fatty acids were significantly different in unadjusted analyses, EPA, the n-6 fatty acid docosapentaenoic acid (DPA), and the n-6 fatty acid dihomo- -linolenic acid (DGLA). Of these only EPA and DPA were significantly related to 2-year mortality after adjustment for the GRACE score (Table 1; see below), hence subsequent analyses focused only on these two.

To determine whether the relationships with 2-year mortality for EPA and DPA were continuous or not, Martingale residuals were constructed (Figures 1a and 1b). Higher levels of EPA and lower levels of DPA were associated with a lower risk of death within 2 years (Table 1). For EPA the relationships were non-linear and suggested high-, intermediate-, and low-risk cutpoints (<0.25%, 0.25%–0.8%, and >0.8%, respectively). For DPA, the relationships were approximately linear. Based on these findings, patient characteristics (including demographics, clinical, lipid factors and GRACE score components) by category of RBC EPA (Table 2) and by tertile of RBC DPA (Table 3) were examined. The two fatty acids themselves were inversely related to each other. Kaplan-Meier curves for admission levels of both EPA by categories (Figure 2a) and DPA by tertiles (Figure 2b) showed significant unadjusted associations with 2-yr mortality. The GRACE score was not significantly related to levels of RBC EPA or DPA. EPA levels were inversely related to a history of chronic heart failure and directly related to high-density lipoprotein cholesterol levels and education. DPA was directly associated with serum creatinine and African American race and inversely with education. (A comparison of all demographic, behavioral, medical and treatment variables according to RBC EPA categories and to DPA tertiles is presented in Supplementary Tables 2 and 3, respectively).

Improvements in GRACE Score Discrimination of 2-Year Mortality by RBC Fatty Acids

When adjusted for the GRACE score, an EPA level in the lowest category (<0.25%) had a hazard ratio (95% CI) of 3.71 (1.81, 7.61; p<0.001) relative to the highest category (0.8%), and the intermediate level (0.25% to 0.8%) had a hazard ratio of 1.76 (1.13, 2.75; p=0.013) relative to the highest. A 1-SD increase in RBC DPA had a mortality hazard ratio of 1.232 (1.056, 1.438; p=0.008). Two factors not included in the GRACE score (HDL-cholesterol and C-reactive protein) were also entered into the model. Neither one modified the GRACE score prediction nor the improvement with EPA and DPA (data not shown).

The c-statistic for the model including only EPA and DPA was 0.60 (95% CI=0.55, 0.65). The inclusion of these two RBC fatty acids with the GRACE score improved the discrimination of the GRACE score's c-statistic from 0.75 to 0.77 (p<0.05) (Table 4). The relative incremental discrimination index improved by 19.8% (95% CI, 7.5%, 35.7%) and the absolute IDI improved by 2.2% (0.87%, 3.92%). The improvement in IDI was due almost completely to an improvement in prediction of those that died (2%) whereas the change in probability for survival was more negligible (0.2%). Adding the RBC fatty acids improved the classification of true events by 26% and of true non-events by 5.5%. Together these resulted in a net reclassification index of 31% (15%, 48%). Lastly, calibration chi-squares for the GRACE + fatty acids model [11.67 (p=0.17)] indicated that it, like the GRACE model alone, was well calibrated.

Discussion

Our purpose in this study was not to develop a new GRACE score, but to determine the extent to which information derived from RBC fatty acid analysis might improve upon an already well-validated risk prediction algorithm for MI patients. Our primary finding was that RBC fatty acid data improved the c-statistic and reduced GRACE score misclassification rates. Secondarily, we found that the ability of the GRACE score alone to discriminate those likely to survive (i.e., the c-statistic) can be extended from the originally-validated 6 months to 2 years[2]. Although our findings imply that risk-stratification in MI patients may be improved by adding RBC EPA and DPA levels to the GRACE risk score, our primary point was to demonstrate that potentially important information about health status may be derived from (at least 2 components of) the fatty acid profile of RBC membrane.

Much research is now focused on improving the prognostic accuracy of validated prediction models by including novel risk markers. It has, however, proven difficult to not only improve the c-statistic, but to also improve classification[24;26;27]. In the current study, we have taken the approach recommended by an expert committee of the American Heart Association[21] in which effects on discrimination, IDI, NRI, and calibration were all evaluated. We found that all aspects of the GRACE score prediction were improved by the addition of RBC fatty acids. Importantly, 31% of our population were correctly reclassified by the inclusion of the fatty acids, primarily driven by the 26% of the cohort that GRACE predicted would be alive but who, in fact, died. Some previous attempts to improve on the GRACE score prediction with novel markers have been successful[28;29] whereas others have not[30;31].

Our study confirms and extends the results of the Infarction Prognosis Study from Japan, where plasma EPA levels were found to be predictors of 16-month total mortality in MI patients[32]. Although not directly compared with the GRACE score, several components of the GRACE score were included in their multivariable models. Ueeda et al. reported similar findings for cardiovascular endpoints[33].

In our previous work, we proposed that an RBC EPA+DHA level (the omega-3 index) of at least 8% offer the greatest protection against subsequent death from CHD[34]. Mortality data from the Heart and Soul study supported this view[5] as do data from case-control studies of ACS and acute MI patients[35;36]. Our data are also consistent with other studies showing an association between lower omega-3 index and sudden cardiac death and/or non-fatal MI[35;37;38]. Our findings support those of a Norwegian study showing that a low omega-3 index was associated with increased risk for in-hospital ventricular fibrillation in MI patients[39], and, among frail[40] elderly patients (mean age 82 years) acutely admitted to the hospital for any cause, 3-year mortality was higher among patients with plasma EPA levels in the lowest quartile[41]. Although our findings agree with those of another Norwegian study in showing no significant relationship between 2-year mortality and the omega-3 index in post-MI patients[42], the Norwegian study did not further examine individual fatty acids (e.g., EPA) nor compare them with GRACE score predictions. In patients without known history of CV disease, lower blood levels of long-chain n-3 fatty acids are associated with an increased risk of sudden death[37;38].

A particularly compelling aspect of using the EPA level to risk-stratify patients is that it is modifiable. A recent study in patients after coronary artery bypass surgery reported by Benedetto et al. found that in those prescribed omega-3 fatty acids at discharge, 2.5-year mortality was reduced by almost 50%[43]. Higher plasma EPA levels (caused by 1.8 g/d EPA supplementation for 5 years) were also associated with reduced major cardiac events in the Japan EPA Lipid Intervention Study[44]. Similarly, treatment with about 1 g/d of EPA+DHA in the GISSI-Prevenzione [7] and GISSI Heart Failure[45] trials also significantly reduced all-cause mortality, although a recent study from Germany reported no benefit on total mortality in post-MI patients after 1 year of treatment with the same dose of EPA+DHA.[8] This latter study, however, was severely underpowered, suggesting that the preponderance of evidence still supports the potential value of EPA+DHA supplementation in post-MI patients. Our findings suggest that this benefit may be most beneficial in those with an EPA level below 0.25%.

The median omega-3 index and EPA levels in our study were 4.9% and 0.6%, respectively, which are consistent with other studies from the US[16;19;46]. In Japan, where fish and seafood are more common components of the diet, the average omega-3 index is twice as high and the RBC EPA level is 2–3 times higher[47;48]. Compared to an estimated life expectancy of 78.4 years in the US, life expectancy in Japan is 82.3 years; 2011 world rankings of 50th and

5th, respectively [49]. The reasons for this 4-year difference in longevity are undoubtedly numerous, however, higher plasma omega-3 levels have been identified as an important correlate of reduced atherosclerotic burden among Japanese men [50].

The mechanisms through which omega-3 fatty acids reduce mortality after MI are not entirely clear. However, a direct cardio-protective effect of omega-3 fatty acids by their incorporation into myocardial cell membranes is thought to play a role[51]. Mechanisms suggested to mediate this cardio-protective effect have recently been reviewed[52] and include altering membrane potentials; affecting sodium and calcium channels, which can reduce susceptibility to arrhythmias); reducing platelet aggregation and thrombin generation; lowering levels of circulating inflammatory markers; and affecting vagal tone, which can reduce heart rate. Recent mouse studies from our lab found potential anti-fibrotic effects[53]. In acute MI patients from Japan, there was a negative correlation between serum levels of omega-3 fatty acids and coronary artery plaque burden[54], and omega-3 supplementation reduces the inflammatory cell burden of carotid plaques[55;56]. Omega-3 fatty acids blood levels have been inversely associated with the rate of telomere attrition[57], a putative measure of cellular aging.

The mechanism(s) by which increased levels of DPA may influence mortality risk are far less clear. DPA n6 is the ultimate fatty acid metabolite of arachidonic acid (C20:4 n6), and is present, like EPA, in the cell membranes in quite low quantities. For example, DPA comprises 0.8% of the fatty acid composition of the RBC cell membrane, compared to 0.6%for EPA, 4.4% for DHA and 20% for arachidonic acid. DPAn6 tends to be inversely associated with DHA and has been proposed as a marker of functional DHA deficiency[58]. There are no known functional metabolites of DPA (such as prostaglandins, leukotrienes, resolvins, neuroprotectins, etc.), and it is not known to be a substrate for cyclooxygenase, lipoxygenase, or cytochrome P450. So the effects of higher (vs lower) DPA levels on inflammatory processes is unknown. In the current study we speculate that DPA may be a marker of functional omega-3 deficiency; whether DPA is a CV risk predictor independent of EPA/DHA is uncertain.

Strengths and Limitations

The main strengths of this study were its relatively large sample size, multi-center design, long-term follow-up, focus on total mortality, comparison with an established risk prediction model (GRACE), and the use of a validated biomarker of fatty acid status. Its limitations were its observational design, the lack of disease-specific endpoints, and the potential for unmeasured confounding. Further studies are required to determine whether utilizing RBC fatty acid measures in risk stratification will lead to increased recommendations for raising omega-3 intakes in the high risk groups or more aggressive treatment (e.g. intra-cardiac defibrillators or revascularization), and more importantly, whether improved risk stratification can reduce mortality.

In conclusion, we found that levels of two relatively minor fatty acid components of RBC membranes (EPA and DPAn6) added significantly to the ability of the GRACE score to predict risk for 2 year mortality in MI patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

CAD	coronary artery disease
CHD	coronary heart disease
CV	cardiovascular
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EDTA	ethylenediaminetetraacetic acid
EPA	eicosapentaenoic acid
GRACE	Global Registry of Acute Coronary Events
MI	myocardial infarction
RBC	red blood cells
TRIUMPH	Translational Research Investigating Underlying disparities in recovery from acute Myocardial infarction
US	United States

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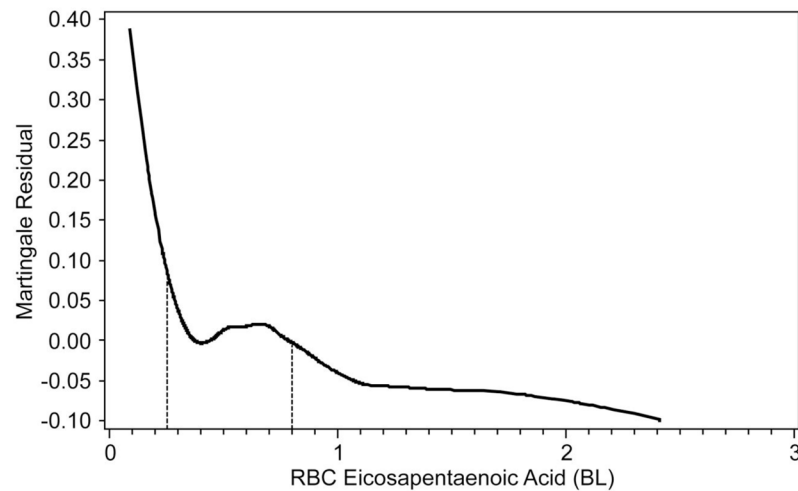
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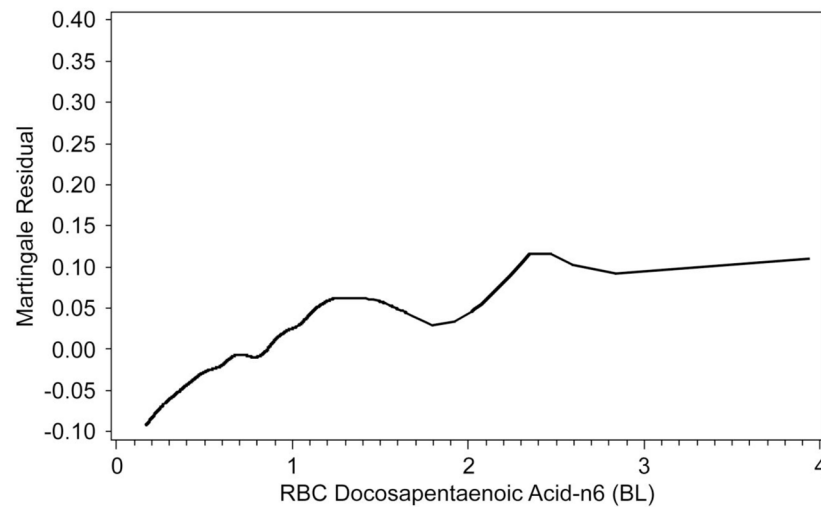
Figure 1B

Figure 1.
The Martingale residual plots show the difference between the observed and predicted (by
GRACE score) 2-year mortality as a function of two RBC fatty levels: A) eicosapentaenoic
acid (EPA) and B) n-6 docosapentaenoic acid (both expressed as a % of total RBC fatty
acids). Values above 0 represent more deaths than predicted, and those below, fewer deaths
than predicted. The relationship between EPA and risk was non-linear, therefore cut points
(vertical lines) were selected to estimate high (<0.25%), intermediate (0.25% and 0.8%) and
low risk categories (>0.8%). Therefore, EPA was modeled as a categorical variable.
Relationships with DPA were relatively linear, therefore this fatty acid was modeled as a
continuous variable.

Figure 2A

Figure 2B

Figure 2.
Kaplan-Meier curves describing the unadjusted mortality by A) RBC EPA cutpoints (log rank p<0.001), and B) RBC DPA tertiles (log rank p=0.018).
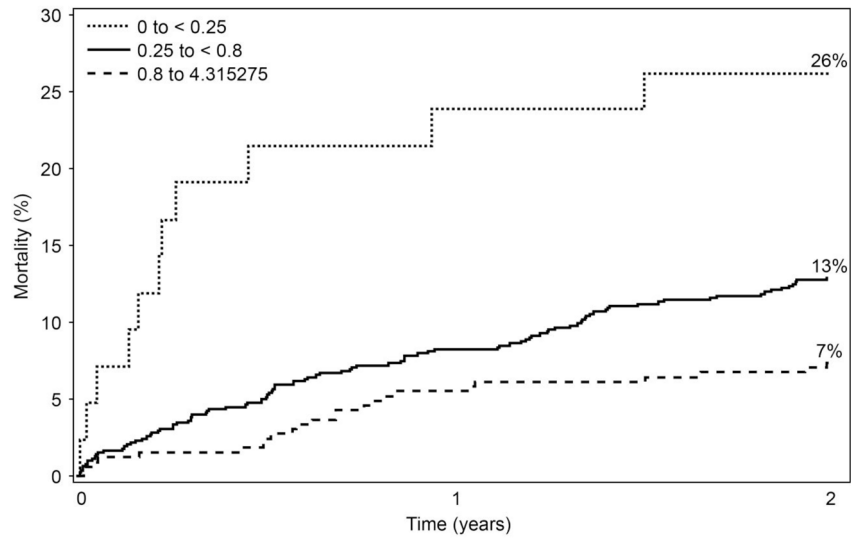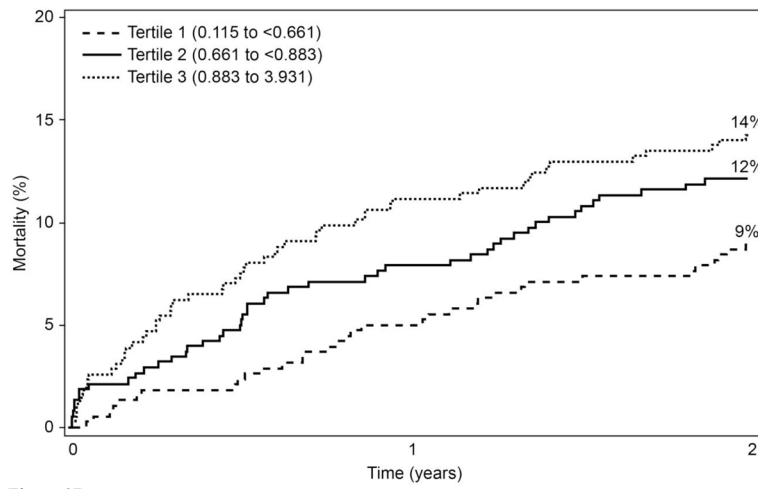
Table 1

Red blood cell fatty acids [median (IQR)] as predictors of 2 year mortality, alone and adjusted for GRACE score

RBC Fatty Acid	Status at 2 years		Fatty Acids Alone		With GRACE Score	
	Dead n = 135	Alive n = 1009	Hazard Ratio Unadjusted	Prop Hazard p-value Unadjusted	Hazard Ratio Adjusted	Prop Hazard p-value Adjusted
Myristic	0.188 (0.148, 0.264)	0.222 (0.148, 0.312)	0.273 (0.073, 1.018)	0.0531	0.443 (0.119, 1.64)	0.2225
Palmitic	20.119 (18.510, 21.451)	20.004 (18.477, 21.380)	0.989 (0.923, 1.059)	0.7504	0.992 (0.923, 1.066)	0.8207
Palmitoleic	0.421 (0.300, 0.604)	0.471 (0.331, 0.667)	0.817 (0.596, 1.12)	0.2097	0.861 (0.647, 1.146)	0.3052
Stearic	15.558 (14.517, 16.725)	15.815 (14.785, 17.002)	0.942 (0.863, 1.028)	0.1769	0.96 (0.882, 1.045)	0.3455
Oleic	14.761 (13.621, 16.169)	14.592 (13.379, 15.816)	1.06 (0.992, 1.134)	0.0869	1.028 (0.959, 1.102)	0.4437
Linoleic	12.879 (11.789, 13.826)	13.287 (11.803, 14.661)	0.91 (0.842, 0.983)	0.0169	0.957 (0.883, 1.037)	0.2795
-Linolenic	0.080 (0.053, 0.116)	0.091 (0.061, 0.132)	2.158 (0.446, 10.434)	0.3386	2.901 (0.705, 11.942)	0.1401
-Linolenic	0.159 (0.116, 0.191)	0.158 (0.118, 0.215)	1.123 (0.283, 4.456)	0.8694	1.025 (0.224, 4.693)	0.9746
Eicosenoic	0.148 (0.110, 0.214)	0.135 (0.102, 0.186)	2.38 (0.748, 7.567)	0.1418	1.173 (0.318, 4.32)	0.8108
Eicosadienoic	0.292 (0.217, 0.376)	0.262 (0.211, 0.345)	1.217 (0.756, 1.957)	0.4190	1.334 (0.8, 2.224)	0.2686
Dihomo- -linolenic	1.562 (1.284, 1.809)	1.639 (1.388, 1.996)	**0.51 (0.346, 0.752)**	**0.0007**	0.678 (0.455, 1.008)	0.0547
Arachidonic	20.195 (18.675, 22.039)	19.959 (18.340, 21.470)	1.07 (0.999, 1.146)	0.0543	1.041 (0.973, 1.113)	0.2486
Eicosapentaenoic	0.552 (0.382, 0.746)	0.607 (0.408, 0.858)	**0.508 (0.302, 0.854)**	**0.0106**	**0.524 (0.312, 0.88)**	**0.0145**
Docosatetraenoic	4.164 (3.480, 4.669)	3.942 (3.329, 4.497)	1.13 (0.99, 1.29)	0.0697	1.109 (0.957, 1.285)	0.1679
Docosapentaenoic n-6	0.835 (0.654, 1.004)	0.767 (0.616, 0.942)	**1.599 (1.038, 2.465)**	**0.0334**	**2.002 (1.257, 3.187)**	**0.0035**
Docosapentaenoic n-3	2.793 (2.368, 3.298)	2.824 (2.400, 3.254)	0.971 (0.772, 1.222)	0.8029	1.041 (0.825, 1.313)	0.7357
Docosahexaenoic	4.364 (3.469, 5.442)	4.267 (3.445, 5.306)	1.073 (0.958, 1.201)	0.2246	1.004 (0.889, 1.134)	0.9438
Omega-3 Index *	4.921 (3.994, 6.164)	4.859 (3.981, 6.055)	1.021 (0.924, 1.13)	0.6788	0.968 (0.868, 1.08)	0.5643
n3/n6 ratio	0.289 (0.239, 0.346)	0.286 (0.245, 0.349)	0.701 (0.123, 3.994)	0.6887	0.479 (0.078, 2.953)	0.4279
n3HUFA/total HUFA †	0.224 (0.193, 0.257)	0.222 (0.197, 0.259)	0.464 (0.018, 12.235)	0.6455	0.214 (0.007, 6.402)	0.3741

*
sum of eicosapentaenoic and docosahexaenoic acids;

†
highly unsaturated fatty acids, i.e., >C18 and >2 double bonds.

Table 2

Subject characteristics by category of Red Blood Cell (RBC) Eicosapentaenoic Acid (EPA, % total fatty acids)

	Total n = 1144	0 to <0.25% n = 42	0.25 to <0.8% n = 776	0.8 to 4.32% n = 326	P-value
GRACE 6-mo Mortality Risk Score	101.3 ± 30.6	102.7 ± 33.4	100.6 ± 31.4	102.8 ± 28.2	0.975
Age (yr)	59.5 ± 12.5	58.6 ± 11.2	58.8 ± 12.9	61.3 ± 11.7	0.198
History of Chronic Heart Failure	107 (9.4%)	7 (16.7%)	77 (9.9%)	23 (7.1%)	0.036
History of Myocardial Infarction	244 (21.3%)	9 (21.4%)	169 (21.8%)	66 (20.2%)	0.613
Heart Rate (beats/min)	82.6 ± 21.3	82.1 ± 18.9	83.5 ± 22.4	80.6 ± 18.7	0.666
Systolic Blood Pressure (mm Hg)	141.2 ± 29.2	142.6 ± 24.2	140.7 ± 29.7	142.0 ± 28.6	0.906
ST-Depression on Admitting EKG	419 (38.4%)	15 (36.6%)	281 (38.3%)	123 (38.9%)	0.773
Creatinine (mg/dL)	1.2 ± 1.1	1.4 ± 1.5	1.2 ± 1.0	1.2 ± 1.2	0.249
In-Hospital PCI	759 (66.3%)	27 (64.3%)	511 (65.9%)	221 (67.8%)	0.494
Sex					0.708
Male	753 (65.8%)	30 (71.4%)	503 (64.8%)	220 (67.5%)	
Female	391 (34.2%)	12 (28.6%)	273 (35.2%)	106 (32.5%)	
Race					0.106
White/Caucasian	809 (70.8%)	28 (66.7%)	535 (69.0%)	246 (75.7%)	
Black/African-American	250 (21.9%)	10 (23.8%)	186 (24.0%)	54 (16.6%)	
Other	83 (7.3%)	4 (9.5%)	54 (7.0%)	25 (7.7%)	
Education > High School	589 (51.7%)	21 (50.0%)	372 (48.2%)	196 (60.3%)	< 0.001
Body Mass Index (kg/m^2)	29.6 ± 6.5	28.9 ± 7.2	29.7 ± 6.5	29.5 ± 6.4	0.583
Ejection Fraction (%)	48.6 ± 13.4	45.3 ± 13.6	48.2 ± 13.5	50.0 ± 13.0	0.049
RBC EPA (M-IQR)	0.6 (0.4, 0.8)	0.2 (0.2, 0.2)	0.5 (0.4, 0.6)	1.1 (0.9, 1.3)	< 0.001
RBC DPA (M-IQR)	0.8 (0.6, 1.0)	0.9 (0.7, 1.1)	0.8 (0.6, 0.9)	0.7 (0.5, 0.9)	< 0.001

	Total n = 1144	0 to <0.25% n = 42	0.25 to <0.8% n = 776	0.8 to 4.32% n = 326	P-value
RBC EPA + DHA (M-IQR)	4.9 (4.0, 6.1)	3.6 (3.1, 4.7)	4.6 (3.9, 5.5)	6.2 (4.8, 7.5)	< 0.001
Taking fish oil on admission	133 (19.9%)	1 (5.6%)	58 (12.9%)	74 (36.5%)	< 0.001
C-reactive protein	16.7 ± 22.7	52.2 ± 42.7	16.2 ± 22.8	9.5 ± 9.9	0.015
Statin at discharge n (%)	984 (86.0%)	41 (97.6%)	663 (85.4%)	280 (85.9%)	0.378
HDL (mg/dL)	40 ± 11	36 ± 8	40 ± 11	40 ± 11	0.006
LDL (mg/dL)	96 ± 32	94 ± 29	97 ± 33	94 ± 31	0.989
Triglycerides (mg/dL) (M-IQR)	130 (100, 175)	128 (99, 176)	132 (101, 178)	128 (95, 171)	0.730
Total Cholesterol (mg/dL)	157 ± 38	154 ± 40	157 ± 38	156 ± 37	0.794

Continuous variables compared using linear trend test. Categorical variables compared using Mantel-Haenszel trend test, or for data presented as medians and interquartile ranges (M-IQR), Kruskal-Wallis test. DHA, docosahexaenoic acid; EPA, Eicosapentaenoic Acid; DPA, Docosapentaenoic acid; PCI, percutaneous coronary intervention; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.

Table 3

Patient characteristics by tertile of Red Blood Cell (RBC) Docosapentaenoic Acid n-6 (DPA; % of fatty acids)

	Tertile 1 (0.12 to <0.66%) n = 380	Tertile 2 (0.66 to <0.88%) n = 379	Tertile 3 (0.88 to 3.93%) n = 385	P-value
GRACE 6-mo Mortality Risk Score	103.6 ± 31.5	97.9 ± 30.1	102.5 ± 30.0	0.632
Age (yr)	61.0 ± 12.4	58.2 ± 12.8	59.2 ± 12.2	0.055
History of Chronic Heart Failure	37 (9.7%)	26 (6.9%)	44 (11.4%)	0.417
History of Myocardial Infarction	82 (21.6%)	72 (19.0%)	90 (23.4%)	0.541
Heart Rate (beats/min)	81.7 ± 20.4	81.6 ± 19.7	84.6 ± 23.5	0.063
Systolic Blood Pressure (mm Hg)	141.2 ± 28.6	139.6 ± 25.9	142.6 ± 32.5	0.511
ST-Depression on Admitting EKG	142 (39.4%)	145 (40.3%)	132 (35.6%)	0.280
Creatinine (mg/dL)	1.2 ± 0.6	1.2 ± 0.8	1.4 ± 1.6	0.002
In-Hospital PCI	261 (68.7%)	259 (68.3%)	239 (62.1%)	0.053
Sex				0.122
Male	261 (68.7%)	248 (65.4%)	244 (63.4%)	
Female	119 (31.3%)	131 (34.6%)	141 (36.6%)	
Race				< 0.001
White/Caucasian	299 (78.9%)	277 (73.1%)	233 (60.7%)	
Black/African-American	50 (13.2%)	84 (22.2%)	116 (30.2%)	
Other	30 (7.9%)	18 (4.7%)	35 (9.1%)	
Education greater than High School	212 (56.1%)	199 (52.5%)	178 (46.6%)	0.009
Body Mass Index (kg/m^2)	29.5 ± 6.0	30.0 ± 6.7	29.3 ± 6.6	0.742
Ejection Fraction (%)	47.9 ± 13.5	49.5 ± 13.0	48.5 ± 13.8	0.551
RBC EPA (M-IQR)	0.7 (0.4, 1.0)	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	< 0.001
RBC DPA (M-IQR)	0.5 (0.4, 0.6)	0.8 (0.7, 0.8)	1.0 (0.9, 1.2)	< 0.001
RBC EPA+DHA (M-IQR)	5.3 (4.0, 6.7)	4.5 (3.8, 5.4)	5.0 (4.1, 5.9)	< 0.001
Taking fish oil on admission	81 (33.6%)	31 (14.2%)	21 (10.0%)	< 0.001
C-reactive protein	17.7 ± 21.3	8.6 ± 9.1	19.2 ± 31.4	0.888
Statin at discharge n (%)	325 (85.5%)	328 (86.5%)	331 (86.0%)	0.859
HDL (mg/dL)	40 ± 11	40 ± 10	40 ± 11	0.762
LDL (mg/dL)	94 ± 30	99 ± 32	94 ± 33	0.993

	Tertile 1 (0.12 to <0.66%) n = 380	Tertile 2 (0.66 to <0.88%) n = 379	Tertile 3 (0.88 to 3.93%) n = 385	P-value
Triglycerides (mg/dL) (M-IQR)	134 (104, 182)	133 (103, 181)	124 (93, 172)	0.091
Total Cholesterol (mg/dL)	156 ± 37	160 ± 38	154 ± 39	0.725

See Table 2 for Total column. Continuous variables compared using linear trend test.

Categorical variables compared using Mantel-Haenszel trend test, or for data presented as medians and interquartile ranges (M-IQR), Kruskal-Wallis test. DHA, docosahexaenoic acid; EPA, Eicosapentaenoic Acid; DPA, Docosapentaenoic acid; PCI, percutaneous coronary intervention; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.

Table 4

Model Parameters comparing GRACE alone to GRACE+EPA+DPA

Metric	GRACE vs GRACE+EPA+DPA
C stat from Grace alone to + FAs	0.747 vs 0.768 (p=0.047)
Incremental Discrimination Index (IDI)	0.022 (0.0087,0.0392)
Relative IDI	0.198 (0.079, 0.357)
Net Reclassification Index	0.314 (0.152, 0.481)
% events correctly reclassified	25.9%
% non-events correctly reclassified	5.46%
Calibration Chi-sq	12.53 and 11.67 (p=0.129 and 0.167)
Proportional Hazards Regression Model HR (Hazard Ratio with 95% CI)	GRACE score alone (p<0.001) For EPA: <0.25% vs >0.8%; HR=3.71 (1.816,7.61) p=0.0004 0.25%–0.8% vs >0.8%; HR=1.76 (1.13,2.75) p=0.013 For DPA (per 1 SD increase): HR=1.23 (1.06, 1.44) p=0.0081