The Influence of Anemia After Percutaneous Coronary Intervention on Clinical Outcomes

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ABSTRACT

Background: Although the consequences of bleeding after percutaneous coronary intervention (PCI) are well documented, there are no data on the impact of post-PCI anemia (PPA) on clinical outcomes.

Methods: We evaluated the incidence, predictors, and prognostic implications of PPA on clinical outcomes in 1415 PCI procedures. We compared clinical outcomes of patients with PPA (ie, nadir post-PCI hemoglobin $<$10 gm/dL) vs without PPA. In patients with PPA, we assessed the influence of thrombolysis in myocardial infarction (TIMI; major or minor) bleeding, drop in hemoglobin by $\geq$3 gm/dL, and use of blood transfusions on outcomes.

Results: Post-PCI anemia developed in 124 (8.8%) patients. Of these, 50 (40%) suffered TIMI (major or minor) bleeding, 68 (55%) had a hemoglobin drop of $\geq$3 gm/dL, and 39 (32%) patients received blood transfusions. Compared to patients without PPA, those with PPA had greater incidence of 6 month death (6.5% vs 1.7 %, $p = 0.003$), 6 month major adverse cardiovascular event (MACE; death, reinfarction, or target vessel revascularization; 27.3% vs 14.5%, $p = 0.0006$), and long-term mortality (25.8% vs 8.7 %, $p \leq 0.0001$). After adjustment for baseline differences, PPA showed an independent association with 6 month MACE (odds ratio [OR]: 2.4, 95% confidence interval [CI]: 1.5–3.9) and long-term mortality (hazard ratio [HR]: 1.3, 95% CI: 1.0–1.6). In patients who developed PPA, the occurrence of TIMI (major or minor) bleeding, hemoglobin drop of $\geq$3 gm/dL, and use of blood transfusions did not impact outcomes.

conclusion: We found that PPA is common, occurs frequently in the absence of bleeding or significant drop in hemoglobin, and connotes poor long-term outcomes.

Introduction

In patients undergoing percutaneous coronary intervention (PCI) for stable or unstable coronary syndromes, antiplatelet and anticoagulant agents are frequently utilized to minimize ischemic complications. These agents are associated with significant risk of bleeding complications and anemia.[1,2] Although the consequences of post-PCI bleeding are well documented, the clinical correlates and consequences of post-PCI anemia (PPA) have not previously been studied. We performed this study to characterize the incidence and predictors of PPA and assess the impact of PPA on clinical outcomes in a mixed population of patients undergoing PCI.

Methods

Study Population

Of 1512 patients who underwent PCI between July 2001 and December 2003, we excluded 9 patients who required coronary artery bypass graft (CABG) surgery during the same hospitalization, 73 patients with baseline hemoglobin $<$10 gm/dL and 15 patients in whom post-PCI hemoglobin was unavailable. The remaining 1415 patients were included in this analysis (Figure 1).

Data Collection

We prospectively collected data on baseline clinical and angiographic characteristics, laboratory values (including hemoglobin before and after PCI during hospitalization), and in-hospital outcomes (death, post-PCI infarction or reinfarction, and target vessel revascularization) on all PCI patients. Evaluation of the occurrence of thrombolysis in myocardial infarction (TIMI major or minor)[3] bleeding was performed by review of patient records and assessment of nadir hemoglobin and use of blood transfusions following PCI. The TIMI bleeding definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 gm/dL or 3%, respectively, for each unit of blood transfused. Therefore, if blood was transfused before obtaining the post-PCI nadir hemoglobin value,

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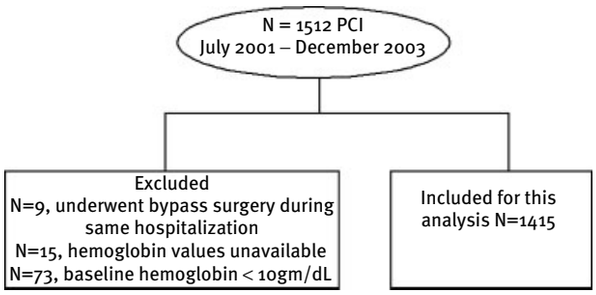

Figure 1. Selection of patients for this analysis.

the true change in hemoglobin was calculated as (pre-PCI hemoglobin minus nadir post PCI hemoglobin) plus (number of units transfused). For example, if pre-PCI and post-PCI hemoglobin were 12 gm/dL and 9 gm/dL respectively, and the patient received 1 unit of packed red blood cell transfusion before the post-PCI hemoglobin was drawn, the true change in hemoglobin was $(12-9)+1=4$ gm/dL.

Following discharge from the hospital, we collected information annually regarding the occurrence of death, myocardial infarction, or target vessel revascularization from patient medical records or telephone contact with the patient or next of kin. Long-term mortality data was also obtained using the Social Security Death Index. This index has previously been shown to be highly accurate.[4] To further ensure accuracy, we compared the mortality data from this index with that obtained by clinical follow-up. Inconsistencies between the Social Security Death Index and clinical follow-up data were resolved by careful review of the patient medical records. All the data obtained were entered into an Excel spreadsheet, and utilized for outcomes analysis.

Study Definitions

Post-PCI anemia was defined as nadir serum hemoglobin value <10 gm/dL after PCI, during the index hospitalization. Nadir hemoglobin was defined as the lowest hemoglobin post-PCI obtained during the index hospitalization. Baseline hemoglobin was defined as hemoglobin obtained within 1 month prior to the PCI. Major adverse cardiovascular events (MACE) were defined as death from any cause, myocardial infarction (or reinfarction), or target vessel revascularization (TVR) following PCI. Post-PCI outcomes were defined according to the American College of Cardiology—National Cardiovascular Data Registry database. Periprocedural myocardial infarction was defined as evolutionary ST-segment elevations, new Q-waves in 2 or more contiguous leads, new or presumably new left bundle branch block, or increase in CK-MB (or troponin) level to ≥3 times the upper limit of normal. Target vessel revascularization was defined as repeat percutaneous or surgical revascularization of the treated vessel, prompted by recurrence of anginal symptoms or other evidence of myocardial ischemia. TIMI major bleeding was defined as intracranial hemorrhage or a ≥5 g/dl decrease in the hemoglobin concentration or a ≥15% absolute decrease in the hematocrit. TIMI minor bleeding was defined as an observed blood loss with ≥3 g/dL decrease in the hemoglobin concentration or a ≥10% decrease in the hematocrit; or no observed blood loss with ≥4 g/dL decrease in the hemoglobin concentration, or a ≥12% decrease in the hematocrit.[3]

Study Outcomes

We evaluated the impact of PPA on 6 month death, 6 month MACE, and death at long-term follow-up. In the subset of patients with PPA, we also evaluated the influence of TIMI (major or minor) bleeding, post-PCI drop in serum hemoglobin ≥3 gm/dl, and use of packed red blood cell transfusions on study outcomes.

Statistical Analysis

Categorical variables are presented as percentages and frequencies, and are compared using the χ^2 statistics or a Fisher's exact *t* test. Continuous variables are presented as means (±1 SD) and are compared using the unpaired *t* test or Mann-Whitney test. To assess independent predictors of PPA, we performed multivariable logistic regression analysis using pertinent clinical variables including age, gender, history of diabetes mellitus, peripheral artery disease, prior coronary artery bypass graft (CABG) surgery, acute coronary syndromes (unstable angina or myocardial infarction), cardiogenic shock, urgency of procedure, positive biomarkers, baseline serum hemoglobin, calculated creatinine clearance (<60 ml/min vs ≥60 ml/min), presence of multivessel disease, intra-coronary stent implantation, and intra-aortic balloon pump (IABP) placement. The independent influence of PPA on study outcomes was assessed using multivariable logistic regression analysis (for 6 month outcomes) and Cox proportional hazards regression for long-term all-cause mortality. All of the above variables, as well as the occurrence of PPA, were included as correlates in these models. Variables that were significant at $p<0.05$ were considered statistically significant. Statview version 5.0.1 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Baseline clinical and angiographic characteristics of patients are shown in Table 1. The mean age of study population was 64 years, over 70% of the patients were males, 95% received IIb/IIIa inhibitors during the index hospitalization and 9% received thrombolytics prior to PCI. Mean baseline hemoglobin before PCI was 13.9 gm/dL, mean nadir

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Table 1. Comparison of Patients with PPA to Those Without PPA

Patient Characteristics	All Patients (n = 1415)	With PPA (n = 124)	Without PPA (n = 1291)	*p* Value
Mean age, years	64±12	70±12	63±11	<0.0001
Age >65 years	644 (46)	80 (65)	564 (44)	<0.0001
Females	423 (30)	78 (63)	345 (27)	<0.0001
Diabetes mellitus	354 (25)	40 (32)	314 (24)	0.06
PAD	222 (16)	29 (23)	193 (15)	0.014
Prior myocardial infarction	403 (28)	30 (24)	373 (29)	0.29
Current smoking	356 (25)	27 (22)	329 (26)	0.02
Prior PCI	449 (32)	16 (13)	433 (34)	<0.0001
Prior bypass surgery	264 (19)	16 (13)	248 (19)	0.09
Baseline hemoglobin, gm/dL	13.9±1.6	12.1±1.3	14.1±1.4	<0.0001
Drop in hemoglobin, gm/dL	1.2±1.3	3.3±1.5	0.9±1	<0.0001
Baseline creatinine clearance, ml/min	90±39	72±44	92±38	<0.0001
ACS (unstable angina or NSTEMI)	741 (52)	55 (44)	686 (53)	0.06
STEMI	288 (20)	50 (40)	238 (19)	<0.0001
Positive troponin before PCI	581 (41)	81 (65)	500 (39)	<0.0001
Cardiogenic shock	30/1384 (2.2)	12/121 (9.9)	18/1263 (1.4)	<0.0001
Received thrombolytic before PCI	128 (9.1)	18 (14.5)	110 (8.5)	0.026
Received glycoprotein IIb/IIIa inhibitors	1316 (93)	114 (92)	1202 (93)	0.65
Received Abciximab	494 (35)	36 (30)	458 (36)	0.17
Urgent procedure	886 (63)	102 (84)	784 (62)	<0.0001
Multivessel disease	914/1384 (66)	85/121 (70)	829/1263 (66)	0.31
Type C lesion	439 (31)	55 (47)	384 (30)	0.0004
Stent used	1242/1388 (90)	108/117 (92)	1134/1271 (89)	0.30
Unplanned intra-aortic balloon pump	73 (5.1)	24 (19)	49 (3.7)	<0.0001
Length of hospitalization, days	2.8±4.4	7.9±12.5	2.3±1.8	<0.0001

Numbers in parenthesis indicate percentages. For variables where data is incomplete, denominators indicate the number of patients with available data and the numerators the number of patients with the characteristic. During study period, unfractionated heparin was the anticoagulant of choice for PCI at our center. Abbreviations: ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPA, post-PCI anemia; STEMI, ST-segmentel elevation myocardial infarction.

hemoglobin was 12.7 gm/dL and 123 patients (8.7%) had a drop in hemoglobin ≥3 gm/dL.

Post-PCI anemia developed in 124 (8.8%) patients. Age >65 years, female gender, lack of prior PCI, lower baseline hemoglobin, greater post-PCI drop in hemoglobin, ST-segment elevation myocardial infarction (STEMI) at presentation, urgency of procedure, type C lesion, and IABP placement showed an univariate association with PPA (Table 1). After adjustment for baseline characteristics, age >65 years, urgent procedure, STEMI, and unplanned IABP were independently associated with PPA (Table 2).

In-hospital outcomes were similar between patients with PPA vs those without PPA (death 1.6% vs 0.9%, MACE 1.6% vs 1.9%, p = not significant [NS] for both). However, patients

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Table 2. Multivariate Predictors of PPA

Predictive Variable	OR	95% CI	*p* Value
Unplanned intra-aortic balloon pump	3.9	1.8–8.2	0.0003
Nonelective procedure	2.4	1.3–4.4	0.0007
ST-elevation myocardial infarction	2.1	1.1–3.5	0.0115
Age >65 years	1.7	1.1–2.8	0.017

Abbreviations: CI, confidence intervals; OR, odds ratio; PCI, percutaneous coronary intervention; PPA, post-PCI anemia.

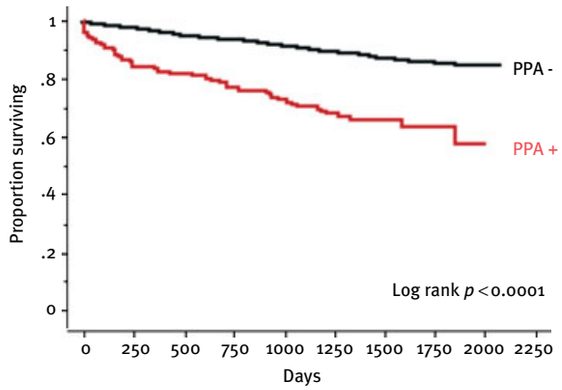

Figure 2. Kaplan-Meier curves representing the estimated survival of patients who developed PPA and those who did not. Abbreviations: PCI, percutaneous coronary intervention; PPA, post-PCI anemia.

with PPA were more likely to suffer death from any cause (6.5% vs 1.7%, $p = 0.003$) and MACE at 6 months (27.3% vs 14.5%, $p = 0.0006$). At a median follow-up of 1473 days (range: 0 to 2086 days, mean: 1424±425 days), death from any cause was more likely to occur in patients with PPA vs those without PPA (35% vs 13%, log rank $p<0.0001$; Figure 2). After adjusting for baseline characteristics, PPA remained an independent risk factor for 6 month MACE (adjusted OR: 2.4, 95% CI: 1.5–3.9) and long-term mortality (adjusted OR: 1.3, 95% CI: 1.1–1.6), but not for 6 month mortality (Figure 3).

Of the patients with PPA, 39 (32%) received blood transfusions (average number of units transfused was 2.1±1.3), 68 (55%) patients had a ≥3 gm/dL drop in hemoglobin after PCI, and 50 (40%) had TIMI (major or minor) bleeding. Among patients with PPA, the use of blood transfusions, presence of TIMI (major or minor bleeding), or hemoglobin drop ≥3 gm/dL had no significant univariate association with 6 month or long-term outcomes (Table 3, Figure 4A,B,C).

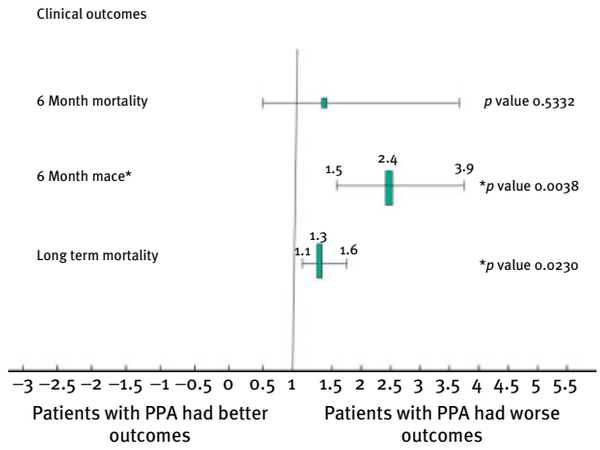

Figure 3. The multivariable impact of PPA on study outcomes. The unadjusted incidence of each study outcome is provided in the groups of patients who developed PPA and those who did not. Adjusted OR and 95% CIs are shown. The *P* values represent the difference between the patients who developed PPA vs those who did not in multivariable analyses. Multivariable predictors of 6 month mortality were cardiogenic shock, baseline creatinine clearance < 60 ml/min, and multivessel disease. Multivariable predictors of 6 month MACE were lack of stent placement, prior CABG, PPA, unplanned IABP use, and nonelective procedures. Multivariable predictors of long-term mortality were diabetes mellitus, prior CABG, unplanned IABP use, and PPA. Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; IABP, intra-aortic balloon pump; MACE, major adverse cardiovascular event; OR, odds ratio; PCI, percutaneous coronary intervention; PPA, post-PCI anemia.

Discussion

Observational data in previous studies has shown that anemia with cardiovascular disease is poorly tolerated and associated with worse short-term outcomes.[5] Previous investigators have described that baseline anemia prior to PCI is associated with increased in-hospital and short-term mortality.[6,7] In contrast to these studies, we evaluated the role of anemia that developed after PCI. Our study has 2 principle findings. First, patients who develop PPA have poor 6-month and long-term outcomes compared to those who do not. PPA is quite common, developing in almost 9% of PCI patients. Age >65 years, urgent procedure, STEMI, and unplanned IABP placement were independent predictors of PPA. Second, amongst patients who develop PPA, the use of blood transfusions, presence of TIMI (major or minor) bleeding, or drop in hemoglobin ≥3 gm/dL does not have any impact on 6 month or long-term clinical outcomes. Further, PPA remained an independent predictor of clinical outcomes after adjustment for several baseline characteristics, including baseline serum hemoglobin. Thus, we believe that the occurrence of PPA may be a stronger marker of adverse outcomes than the presence of anemia prior to PCI.

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Table 3. Clinical Outcomes of Patients with PPA Classified by Occurrence of TIMI (Major or Minor) Bleeding, Drop in Hemoglobin and Use of Blood Transfusions

Outcome	TIMI (major or minor bleeding) +(n = 50)o(n = 74)		*p* Value
6 month death, %	5 (10%)	3 (4.1%)	0.27
6 month MACE,[a] %	16/48 (33%)	17/73 (23%)	0.22
Long-term death, %	17 (34%)	27 (36%)	0.9
	Drop in Hemoglobin ≥3 gm/dL +(n = 68)o(n = 56)		*p* Value
6 month death, %	6 (8.8%)	2 (3.6%)	0.29
6 month MACE,[a] %	20/66 (30%)	13/55 (24%)	0.41
Long-term death, %	24 (35%)	20 (36%)	0.99
	Received Blood Transfusion +(n = 39)o(n = 85)		*p* Value
6 month death, %	3 (7.7%)	5 (5.9%)	0.71
6 month MACE,[a] %	14/38 (37%)	19/83 (23%)	0.11
Long-term death, %	13 (33%)	31 (36%)	0.87

[a]Data on 6 month MACE was available in 121 of 124 patients who developed PPA. Abbreviations: MACE, major adverse cardiovscular event; PCI, percutaneous coronary intervention; PPA, post-PCI anemia; TIMI, thrombolysis in myocardial infarction.

Only 40% of patients with PPA had documented TIMI (major or minor) bleeding, and only 55% exhibited a hemoglobin drop of ≥3 gm/dL after PCI. Thus, PPA developed in a large proportion of patients without documented TIMI (major or minor) bleeding or significant change from baseline hemoglobin value. Multiple prior studies have established an association between post-PCI bleeding and adverse in-hospital and 1 year outcomes.[8–10] Interestingly, amongst the patients with PPA in our study, TIMI (major or minor) bleeding did not have any additional detrimental impact on outcomes. Our findings should not be construed to contradict the role of TIMI (major or minor) bleeding in affecting the outcome of patients after PCI. Rather, our study indicates that lower post-PCI nadir hemoglobin may be a stronger marker of adverse outcomes than the occurrence of bleeding. This conclusion is reinforced by the fact that patients with PPA had poor outcomes irrespective of whether their hemoglobin dropped by ≥3 gm/dL.

Silent perioperative ischemia has been reported in patients with hemoglobin levels between 6 and 10 gm/dL, undergoing cardiac[11] and noncardiac[12] surgery. Among elderly patients with acute myocardial infarction, lower hematocrit values on admission had higher 30 day mortality rates and blood transfusion for admission hematocrit 30% or lower, was associated with a lower short-term mortality rate.[13] In current practice, patients at risk of cardiac ischemia usually receive blood transfusions to keep hemoglobin ≥10 gm/dL. Hence in our study, hemoglobin < 10 gm/dL was used to define PPA.

Kinnaird et al have suggested a restrictive transfusion strategy after PCI.[8] Although blood transfusions increase hemoglobin level and promote better oxygen delivery, they also have deleterious effects on blood viscosity, free radical production, fluid overload, electrolyte abnormalities, hypothermia, and immune suppression which in turn affect cardiac performance.[14–18] In the largest randomized trial to date comparing aggressive vs conservative blood transfusion strategies in critically ill patients with hemoglobin values <7 gm/dL, aggressive use of blood transfusions did not improve 30 day all-cause mortality,[19] or cardiovascular morbidity or mortality.[20] Our findings concur with this conclusion, since use of blood transfusions did not improve clinical outcomes among patients with PPA in our study.

Preoperative anemia in surgical settings, including CABG, hip surgery, and elective vascular surgery, has been shown to have a detrimental impact on operative outcomes.[21–23] Similarly, anemia complicating medical conditions like chronic kidney disease, myocardial infarction, and congestive heart failure have also been associated with poor outcomes.[13,24,25] The adverse impact of anemia concurrent with cardiovascular, medical, or surgical conditions is likely mediated by multiple mechanisms including diminished oxygen delivery to tissues, increased cardiac output resulting in increased myocardial oxygen demand, with resultant myocardial ischemia, as well as the effect of underlying comorbid conditions.[5] Further, the anemia of chronic disease is mediated by proinflammatory cytokines which may accelerate atherosclerosis.[26] Many of these factors likely play a pathophysiologic role in affecting the outcomes of patients who develop anemia in the PCI setting.

Limitations

Our study is an observational single-center study and has significant limitations. We did not seek data on the specific cause of PPA. Thus, in those patients who did not suffer TIMI (major or minor) bleeding, the cause of PPA remains unexplained. Only a small number of patients received transfusion, and the decision to transfuse was dependent on the primary care provider. Therefore, the true impact of blood transfusions on post-PCI outcomes is difficult to assess. Although, multivariable analyses may adjust for the impact of several confounding variables, there may be baseline differences between patients, who did vs those who did not develop PPA, which are not accounted for in our analyses. Despite these limitations, our study offers some unique insights. In contrast to prior studies which addressed the impact of anemia prior to PCI on outcomes,[6,7] we addressed the effect of anemia developing after PCI on

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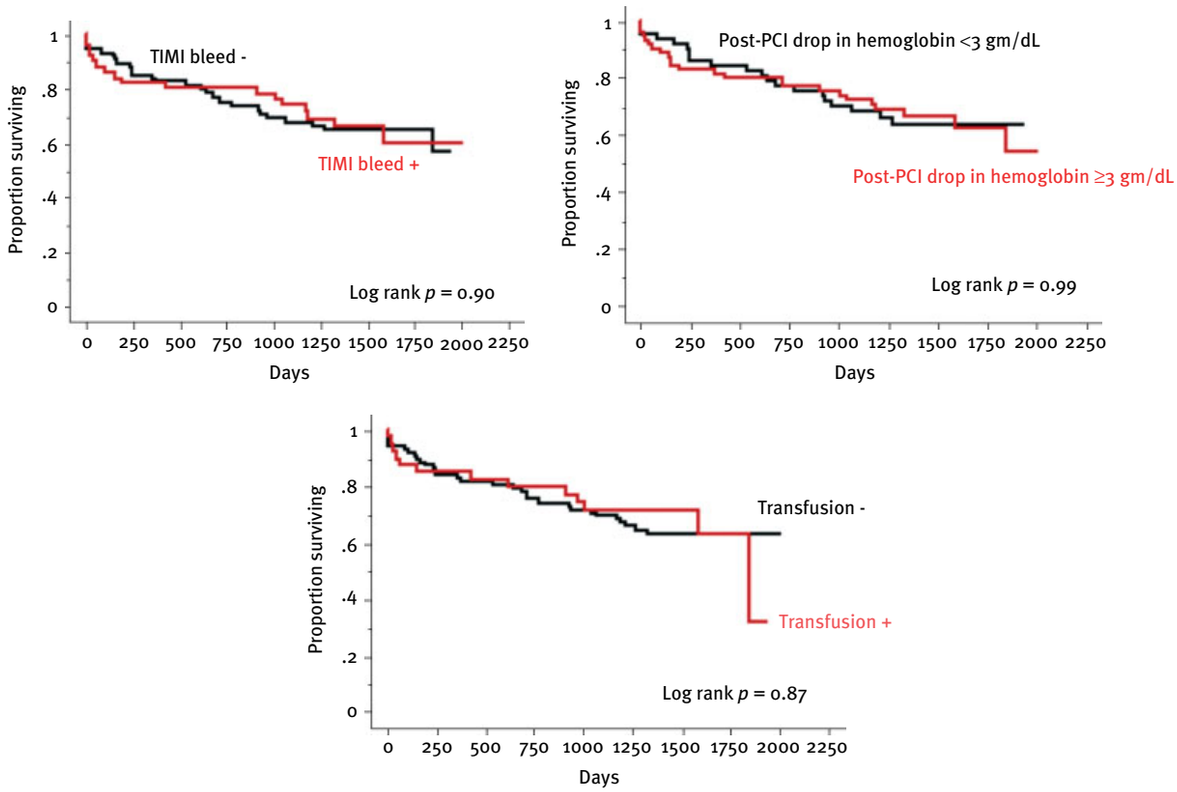

Figure 4. Kaplan-Meier curves representing the estimated survival of patients who developed PPA. The figures represent differences in patients who had TIMI (major or minor) bleeding vs those who did not (A), patients who had a post-PCI drop in hemoglobin of ≥3 gm/dL vs those who did not (B), and patients who received blood transfusions vs those who did not (C). Abbreviations: PCI, percutaneous coronary intervention; PPA, post-PCI anemia; TIMI, thrombolysisin myocardial infarction.

clinical outcomes. Our findings suggest that PPA occurs commonly and is a strong marker of poor adverse outcomes. The prognostic impact of PPA is independent of pre-PCI hemoglobin value, occurrence of TIMI (major or minor) bleeding, drop in hemoglobin by ≥3 gm/dL, and use of blood transfusions.

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