External Validation of the Revised Pretransplant Assessment of Mortality Score in Allogeneic Hematopoietic Cell Transplantation: A Cohort Study

Nicolas Fattinger1,2, Jan A. Roth2,3, Helen Baldomero1,2, Daiana Stolz2,4, Michael Medinger1,2,5, Dominik Heim1,2, Michael Tamm2,4, Jörg P. Halter1,2, Jakob R. Passweg1,2, Martina Kleber1,2,5,6

Correspondence: Martina Kleber (martina.kleber@usz.ch).

ABSTRACT
Pretransplant risk scores such as the revised Pretransplant Assessment of Mortality (rPAM) score help to predict outcome of patients receiving allogeneic hematopoietic cell transplantation (allo-HCT). Since the rPAM has not been validated externally in a heterogeneous patient population with different diseases, we aimed to validate the rPAM score in a real-world cohort of allo-HCT patients. A total of 429 patients were included receiving their first allo-HCT from 2008 to 2015. The predictive capacity of the rPAM score for 4-year overall survival (OS), nonrelapse mortality (NRM), and cumulative incidence of relapse (CIR) after allo-HCT was evaluated. Moreover, we evaluated the impact of the rPAM score for OS and used uni- and multivariable analyses to identify patient- and transplant-related predictors for OS. In rPAM score categories of <17, 17–23, 24–30, and >30, the OS probability at 4 years differed significantly with 61%, 36%, 26%, and 10%, respectively (P < 0.0001). In contrast to CIR, the NRM increased significantly in patients with higher rPAM scores (P < 0.001). Regarding the OS, the rPAM score had an area under the receiver operating characteristics curve of 0.676 (95% confidence interval [CI], 0.625–0.727) at 4 years. In the multivariable analysis, the rPAM score was associated with OS—independently of conditioning regimens (adjusted hazard ratio per 1-unit increase, 1.10; 95% CI, 1.06–1.10; P < 0.001). Additionally, forced expiratory volume in 1 second and the disease risk index were the components of the rPAM significantly associated with outcome. In our large real-world cohort with extended follow-up, the rPAM score was validated as an independent predictor of OS in patients with hematologic disorders undergoing allo-HCT.

INTRODUCTION
Allogeneic hematopoietic cell transplantation (allo-HCT) has become a standard treatment for numerous malignant and nonmalignant hematologic disorders.1–3 Patient outcomes have improved over the last years, but allo-HCT is still associated with substantial transplant-related morbidity and mortality.4–7 Therefore, evaluation of the patient- and disease-related safety profiles is essential to balance harms and benefits of allo-HCT.8 Different scores to predict outcome after HCT have been developed. For comorbidity measurement, the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) is a well-established weighted comorbidity score, which reflects organ dysfunction with 17 comorbidities to predict nonrelapse mortality (NRM) and overall survival (OS) after HCT.9,10 In contrast, the European Society for Blood and Marrow Transplantation (EBMT) pretransplantation risk score combines disease- and transplant-related risk factors by including variables such as age, disease stage, time from diagnosis, donor type, and donor–recipient sex combinations, but it does not account for comorbidities.11 The Pretransplant Assessment of Mortality (PAM) score was originally developed in 2006 to predict all-cause mortality after HCT and included the following 8 items: age, donor type, disease risk, conditioning regimen, serum creatinine, serum alanine aminotransferase, forced expiratory volume in 1 second (FEV1), and carbon monoxide diffusing capacity of the lung.12 The advantage of this score is incorporating actual laboratory values to represent organ function instead of score based on dichotomized patient narratives. Due to evolving allo-HCT strategies with more frequent application of non-myeloablative conditioning regimens (MAC), the PAM score was re-evaluated and simplified 9 years later13: While serum creatinine, serum alanine aminotransferase, and carbon monoxide diffusing capacity were no longer identified as risk factors in allo-HCT, patient and donor cytomegalovirus (CMV) serology were associated with OS and added to the PAM score. The revised PAM (rPAM) score has been validated in a cohort of patients with acute
myelogenous leukemia receiving allo-HCT where it was associated with all-cause mortality, cumulative incidence of relapse (CIR), and NRM. However, since the rPAM score has not been validated externally in allo-HCT cohorts covering a wider spectrum of diseases, we aimed to validate the rPAM score in a real-world cohort of patients with an extended follow-up.

MATERIAL AND METHODS

Patient population and study design

We conducted a cohort study at the Division of Hematology, University Hospital Basel: From 2008 to 2015, consecutive patients receiving a first allo-HCT to treat hematological disorders were included. Patients with a missing rPAM score (15 of 429 patients) were excluded from the final analyses. The study period was chosen to allow a reasonable long-term follow-up of the patients.

We conducted the study according to the Declaration of Helsinki. Our study was approved by the Ethics Committee of Northwestern and Central Switzerland (EKNZ project number 2015-449).

Conditioning regimens and graft-versus-host disease prophylaxis

MAC included cyclophosphamide plus busulfan (n = 148), cyclophosphamide with total body irradiation (TBI) >8 Gy (n = 87), and other protocols (n = 95). Reduced conditioning regimens (RIC) consisted of fludarabine with low-dose TBI ≤6 Gy (n = 62), fludarabine plus busulfan (n = 26), and other protocols (n = 11). Reasons for RIC were advanced age or relevant comorbidities.15 Graft versus host disease (GvHD) prophylaxis administered along with the MAC was cyclosporine A and methotrexate as well as anti–T-cell globulins (ATG) in case of an unrelated donor. In patients with RIC, the GvHD prophylaxis consisted of cyclosporine A, methotrexate, and ATG in case of an unrelated donor. In matched related donors ≥40 years, GvHD prophylaxis was performed according to institutional standards (if RIC was fludarabine/busulfan) or cyclosporine A and mycophenolate mofetil (if RIC was fludarabine/low-dose TBI).15

Pretransplantation assessment and definition

As depicted in Table 1, we analyzed patient-, disease-, and transplant related variables including all variable required to calculate the rPAM score.12,13 Based on pretransplant patient characteristics transplant-related risk factors, comorbid conditions, and the patient performance were scored. We calculated the rPAM score via an online calculator (http://pamscore.org/) dividing the study population into four risk categories: rPAM score <17, rPAM score 17–23, rPAM score 24–30, and rPAM score >30, based on the original studies of the patients receiving a first allo-HCT where it was associated with all-cause mortality, cumulative incidence of relapse and NRM.14 However, since the rPAM score has not been validated externally in allo-HCT cohorts covering a wider spectrum of diseases, we aimed to validate the rPAM score in a real-world cohort of patients with an extended follow-up.

RESULTS

Patient characteristics

Of the 429 patients studied, the median age was 54 years (IQR, 43–61 years). Median follow-up of surviving patients was 62 months (IQR, 13–124 months). Main hematologic diagnoses were myeloid malignancies (59%) and lymphoid malignancies (38%) (Table 1).

Conditioning regimens were largely myeloablative (77%); 23% were reduced intensity regimens. A majority of patients (57%) received cyclosporine and methotrexate, or mycophenolate without ATG, whereas GvHD prophylaxis was ATG based in 43%.

Donor type was mostly related HLA matched donors in 39%, followed by fully HLA matched unrelated donors in 36%. The primary stem cell source was peripheral blood stem cells (91%).

Analysis comparing 4-year-OS, CIR, and NRM

Analysis comparing 4-year-OS, CIR, and NRM are demonstrated in Table 1. In the univariable analysis, the following factors were associated with a reduced OS: age of 63 or more years, higher disease risk, GvHD prophylaxis, KPS <80%, higher HCT-CI and rPAM scores. In patients with different rPAM score categories of <17, 17–23, 24–30, and >30, the OS at 4-year decreased in each rPAM score category from 61% versus 36% versus 26% to 10% (P < 0.001), respectively (Table 1, Figure 1). Correspondingly, the 4-year NRM (P < 0.001, Figure 2) and the 4-year CIR (P = 0.178) increased with an increasing rPAM score (Table 1). Of note, the rPAM score as a continuous variable was not only significant for OS, NRM, but also for CIR (subdistribution hazard ratio of 1.03 [95% confidence interval [CI], 1.001–1.051; P = 0.043]).

In the final, multivariable analysis, non–ATG-based GvHD prophylaxis (adjusted hazard ratio [HR] 1.76; 95% CI, 1.28–2.240; P < 0.001), an impaired performance status of <80% (adjusted HR 1.67; 95% CI, 1.05-2.65; P = 0.031), and the rPAM score (adjusted HR per 1-unit increase 1.10; 95% CI, 1.06-1.10; P < 0.001) were associated with OS within 4 years (Table 2).

To evaluate each component of the rPAM score on OS, we analyzed the rPAM score in a multivariable analysis (Table 3). Results showed that higher DRI and worsening FEV1 levels (displayed as a continuous linear variable and HR representing...
changes in hazard with each decrease in FEV1 by 10%) were the most relevant risk factors for impaired OS. In contrast, age, donor type, and donor/recipient CMV status failed to reach significance in our cohort. Regarding the discrimination of the rPAM for OS within 4 years, an AUROC of 0.676 (95% CI, 0.625-0.727) was observed.

### Table 1.

**Patient Characteristics and 4-y Outcomes After Allogeneic Hematopoietic Cell Transplantation**

| Variables                          | Frequency, n (%) | OS, % (95% CI) | CIR, % (95% CI) | NRM, % (95% CI) |
|-----------------------------------|------------------|----------------|----------------|----------------|
| All patients                      | 429 (100)        | 50 (45-55)     | 36 (32-41)     | 20 (16-24)     |
| **Age (y)**                       |                  |                |                |                |
| <65                               | 377 (88)         | 52 (47-57)     | 38 (33-43)     | 18 (15-22)     |
| ≥65                               | 52 (12)          | 35 (22-49)     | 35 (22-48)     | 33 (21-46)     |
| **P value**                       | 0.041            | 0.791          | 0.018          |                |
| **Diagnosis**                     |                  |                |                |                |
| Myeloid malignancy                | 253 (59)         | 47 (41-53)     | 40 (34-46)     | 19 (14-24)     |
| Lymphoid malignancy               | 164 (38)         | 53 (45-61)     | 36 (30-40)     | 21 (15-28)     |
| Bone marrow failure               | 12 (3)           | 67 (34-86)     | n.a.           | 33 (10-59)     |
| **P value**                       | 0.446            | <0.0001        | 0.365          |                |
| **DRI**                           |                  |                |                |                |
| Low risk                          | 61 (14)          | 74 (61-83)     | 16 (8-27)      | 17 (9-27)      |
| Intermediate risk                 | 304 (71)         | 50 (44-56)     | 39 (34-45)     | 20 (16-25)     |
| High risk                         | 54 (13)          | 30 (18-43)     | 46 (33-59)     | 24 (14-36)     |
| Very high risk                    | 10 (2)           | 30 (7-58)      | 50 (18-75)     | 20 (3-47)      |
| **P value**                       | <0.0001          | 0.005          | 0.743          |                |
| **Conditioning regime**           |                  |                |                |                |
| MAC                               | 330 (77)         | 53 (47-58)     | 35 (30-40)     | 19 (15-24)     |
| RIC                               | 99 (23)          | 41 (31-50)     | 45 (35-54)     | 22 (15-31)     |
| **P value**                       | 0.112            | 0.067          | 0.622          |                |
| **TBI**                           |                  |                |                |                |
| No                                | 247 (58)         | 50 (44-57)     | 38 (32-44)     | 19 (14-24)     |
| Yes                               | 182 (42)         | 50 (42-57)     | 36 (29-43)     | 22 (16-28)     |
| **P value**                       | 0.836            | 0.796          | 0.348          |                |
| **CMV status patient/donor**      |                  |                |                |                |
| Pos/pos                           | 135 (31)         | 46 (37-54)     | 42 (33-50)     | 19 (13-26)     |
| Pos/neg                           | 109 (25)         | 49 (39-58)     | 34 (25-43)     | 22 (15-30)     |
| Neg/pos                           | 41 (10)          | 53 (36-67)     | 32 (18-46)     | 28 (15-42)     |
| Neg/neg                           | 144 (34)         | 55 (46-62)     | 38 (30-46)     | 17 (12-24)     |
| **P value**                       | 0.382            | 0.456          | 0.587          |                |
| **Donor type**                    |                  |                |                |                |
| Related matched                   | 168 (39)         | 55 (47-62)     | 44 (36-51)     | 11 (7-17)      |
| Related mismatched                | 14 (3)           | 43 (14-70)     | 43 (18-66)     | 14 (2-37)      |
| Unrelated matched                 | 152 (36)         | 43 (35-51)     | 35 (27-42)     | 27 (21-35)     |
| Unrelated mismatched              | 95 (22)          | 54 (44-64)     | 29 (20-39)     | 24 (16-33)     |
| **P value**                       | 0.265            | 0.112          | 0.006          |                |
| **GvHD prophylaxis**              |                  |                |                |                |
| Non–ATG-based                     | 246 (57)         | 46 (39-52)     | 39 (33-45)     | 22 (17-27)     |
| ATG-based                         | 183 (43)         | 56 (48-64)     | 35 (28-42)     | 18 (13-24)     |
| **P value**                       | 0.013            | 0.276          | 0.310          |                |
| **KPS (%)**                       |                  |                |                |                |
| <80                               | 31 (7)           | 32 (17-49)     | 48 (30-64)     | 23 (10-38)     |
| ≥80                               | 398 (93)         | 51 (46-66)     | 36 (32-41)     | 20 (16-24)     |
| **P value**                       | 0.001            | 0.068          | 0.658          |                |
| **HCT-CI**                        |                  |                |                |                |
| 0                                 | 155 (36)         | 61 (53-68)     | 31 (24-38)     | 19 (14-26)     |
| 1–2                               | 133 (31)         | 49 (40-58)     | 43 (35-52)     | 14 (9-20)      |
| >2                                | 141 (33)         | 39 (30-47)     | 39 (31-48)     | 27 (20-34)     |
| **P value**                       | <0.001           | 0.042          | 0.032          |                |
| **rPAM score**                    |                  |                |                |                |
| <17                               | 251 (59)         | 61 (55-67)     | 35 (30-42)     | 13 (9-18)      |
| 17–23                             | 112 (26)         | 36 (27-45)     | 41 (31-50)     | 27 (19-35)     |
| 24–30                             | 41 (10)          | 26 (13-40)     | 47 (21-62)     | 35 (21-49)     |
| >30                               | 10 (2)           | 10 (1-36)      | 50 (18-75)     | 40 (12-67)     |
| Missing                           | 15 (3)           |                |                |                |
| **P value**                       | <0.0001          | 0.187          | <0.001         |                |

CI = confidence interval; CIR = cumulative incidence of relapse; CMV = cytomegalovirus; DRI = disease risk index; EBMT = European Group for Blood Marrow Transplantation Risk Score; GvHD = graft-vs-host-disease; HCT-CI = Hematopoietic Cell Transplant Co-Morbidity Index; KPS = Karnofsky Performance Status; MAC = myeloablative conditioning; n.a. = not applicable; NRM = nonrelapse mortality. P values were calculated by using univariate Cox regression models (OS) and competing risk regression models (CIR and NRM); OS = overall survival; rPAM = revised Pretransplant Assessment of Mortality Score; RIC = reduced-intensity conditioning; TBI = total body irradiation.
DISCUSSION

We have validated the rPAM score in a large, real-world allo-HCT cohort. Regarding our primary outcome, we could demonstrate that the rPAM score is an independent predictor of OS in patients undergoing allo-HCT for various hematological disorders. Furthermore, we observed that NRM (but also CIR with the rPAM as a continuous variable) increased substantially with higher rPAM scores.
Table 2.
Uni- and Multivariable Analysis for Overall Survival With the rPAM Score

| Variable                | Univariable Analysis | Multivariable Analysis |
|-------------------------|----------------------|------------------------|
|                         | HR 95% CI            | P Value                |
|                         |                      |                        |
| Conditioning regimens   |                      |                        |
| Myeloablative           | Ref.                 |                        |
| Reduced-intensity       | 1.26 0.94-1.69       | 0.13                   |
| TBI                     | Ref.                 |                        |
| Yes                     | 1.01 0.77-1.31       | 0.06                   |
| No                      | Ref.                 |                        |
| ≥80                     | Ref.                 |                        |
| Non–ATG-based           | 1.38 1.05-1.82       | 0.02                   |
| ATG-based               |                      |                        |
| GvHD prophylaxis        |                      |                        |
| No                      | 1.01 0.77-1.31       | 0.06                   |
| Yes                     | Ref.                 |                        |
| KPS (%)                 |                      |                        |
| ≥65                     | 51 (12)              | 1.40 0.95-2.04         | 0.088 |
| <65                     | 363 (88)             | Ref.                   |      |
| ≥80                     | Ref.                 |                        |
| >80                     | Ref.                 |                        |
| RvPAM score*            | 1.08 1.06-1.10       | <0.001                 |
| Age (y)                 |                      |                        |
| <65                     | 363 (88)             | Ref.                   |      |
| ≥65                     | 51 (12)              | 1.40 0.95-2.04         | 0.088 |
| Donor type              |                      |                        |
| Related matched         | 165 (40)             | Ref.                   |      |
| Related mismatched      | 14 (3)               | 1.41 0.64-3.08         | 0.397 |
| Unrelated matched       | 148 (36)             | 1.32 0.96-1.80         | 0.086 |
| Unrelated mismatched    | 87 (21)              | 1.43 0.97-2.07         | 0.059 |
| Disease risk index      |                      |                        |
| Low risk                | 48 (12)              | Ref.                   |      |
| Intermediate risk       | 302 (73)             | 2.14 1.23-3.71         | 0.007 |
| High risk               | 54 (13)              | 3.41 1.83-6.36         | <0.001|
| Very high risk          | 10 (2)               | 3.33 1.32-8.42         | 0.011 |
| FEV1*                   | 414 (100)            | 1.13 1.05-1.22         | 0.001 |
| CMV status              |                       |                        |
| Neg/neg                 | 140 (34)             | Ref.                   |      |
| Neg/pos                 | 40 (10)              | 1.26 0.88-1.79         | 0.212 |
| Pos/neg                 | 104 (25)             | 1.41 1.01-1.96         | 0.046 |
| Pos/pos                 | 130 (31)             | 0.89 0.52-1.50         | 0.765 |

Number of subjects included in the univariable and multivariable model n = 414.
*ATG used as a continuous variable (HR per 1-unit increase).

Table 3.
Multivariable Analysis of the rPAM Score (n = 414) Variables for OS

| Variable            | Univariable Analysis | Multivariable Analysis |
|---------------------|----------------------|------------------------|
|                     | HR 95% CI            | P Value                |
|                     |                      |                        |
| Age (y)             |                      |                        |
| <65                 | 363 (88)             | Ref.                   |      |
| ≥65                 | 51 (12)              | 1.40 0.95-2.04         | 0.088 |
| Donor type          |                      |                        |
| Related matched     | 165 (40)             | Ref.                   |      |
| Related mismatched  | 14 (3)               | 1.41 0.64-3.08         | 0.397 |
| Unrelated matched   | 148 (36)             | 1.32 0.96-1.80         | 0.086 |
| Unrelated mismatched| 87 (21)              | 1.43 0.97-2.07         | 0.059 |
| Disease risk index  |                      |                        |
| Low risk            | 48 (12)              | Ref.                   |      |
| Intermediate risk   | 302 (73)             | 2.14 1.23-3.71         | 0.007 |
| High risk           | 54 (13)              | 3.41 1.83-6.36         | <0.001|
| Very high risk      | 10 (2)               | 3.33 1.32-8.42         | 0.011 |
| FEV1*               | 414 (100)            | 1.13 1.05-1.22         | 0.001 |
| CMV status          |                      |                        |
| Neg/neg             | 140 (34)             | Ref.                   |      |
| Neg/pos             | 40 (10)              | 1.26 0.88-1.79         | 0.212 |
| Pos/neg             | 104 (25)             | 1.41 1.01-1.96         | 0.046 |
| Pos/pos             | 130 (31)             | 0.89 0.52-1.50         | 0.765 |

4 FEV1 displayed as a continuous linear variable and HR representing changes in hazard with each.
5 CI = confidence interval; CMV = cytomegalovirus; FEV1 = forced expiratory volume in 1 s; HR = hazard ratio; OS = overall survival; rPAM = revised Pretransplant Assessment of Mortality Score.

Allo-HCT offers a curative option for many patients with hematological disorders.20 Despite optimized transplant practice (including supportive care), allo-HCT continues to be associated with considerable transplant-related morbidity and mortality, which differ between patient subgroups. The potential risk for treatment-related complications highlights the importance of balancing the goal of disease control/cure with treatment-related morbidity and mortality. To address these challenges, several prognostic models and scores were developed.14,20,21 Due to the variability of analyzed outcomes, some prognostic scores include disease-related factors to predict relapse (eg, DRI), whereas other integrate patient-related risk factors (eg, HCT-CI) reflecting comorbid conditions predicting transplant-related mortality.16,21 A more universal approach pursues the EBMCT score, which incorporates transplant- and disease-related risk factors22 and the rPAM score with the integrated patient-, disease-, and donor-specific features.13 The rPAM score was originally developed to predict OS, but an external validation of the rPAM score for outcomes such as NRM or CIR has not been performed in detail.14,21 The results of our study support the use of the rPAM score in clinical practice for pretransplant risk stratification in allo-HCT.

The available scores differ substantially in their discriminating capacity.20 for instance, the reported AUROCs for OS within 2 years in allo-HCT were 0.58 (EBMT score), 0.62 (rDRI), 0.55 (HCT-CI), and 0.64 (rPAM score).21 In our cohort, the respective AUC of the rPAM score for OS within 4 years was 0.68. Our results are in line with the discrimination capacity reported by Shouval et al21 in patients with primarily acute myeloid leukemia (2-year AUROC of the rPAM: 0.64) and by Middeke et al14 in a homogenous cohort of acute myeloid leukemia patients (4-year AUROC of the rPAM: 0.703).

In our investigation, the rPAM score was a predictor of OS—indepenent of the conditioning regimen. Previous analyses showed that the rPAM score has more predictive strengths in patients receiving MAC regimens compared to RIC. This could be due to the fact that patients treated with RIC have more often comorbid conditions which are not covered by the rPAM score.13,14 Compared to the current literature, our results support the use of rPAM score independently of treatment intensity.

The prediction capacity of each prognostic model is driven by its components, which implies regular validation of each parameter.20 Previous analyses could demonstrate that the DRI is probably the strongest predictor for allo-HCT outcomes16,21 and therefore the predictive power of the rPAM may be primarily based on the incorporation of the DRI.23 In our multivariable analyses, each component of the rPAM score for OS was analyzed and we could confirm that the higher discrimination of the rPAM score is primarily caused by the incorporation of the DRI and more interestingly by the pretransplant lung function defined by FEV1. The latter demonstrating that comorbid patients-related risk factors such as pulmonary function is an essential diagnostic test to derive an important prognostic conclusion about the validity of the rPAM score.20,24 The rPAM score was originally derived to predict OS. Several validation studies20,21 have also provided encouraging data for the value of rPAM in predicting CIR. Only the DRI was significantly associated with CIR, while age, CMV status, and donor type did not
reach statistical significance, that probably reduce the predictive value of the rPAM with respect to CIR.

In our multivariable analysis, we observed that other prognostic factors (not covered by the EBMT, HCT-CI, or rPAM score) such as non-ATG-based GvHD prophylaxis and an impaired KPS were independent predictors of OS—besides the rPAM score.

Our study has certain limitations including the design as a retrospective single-center study and the heterogeneous study population, the latter also reflecting the strength of a real-world cohort. Additionally, the use of the rPAM score requires pre-transplant pulmonary function testing.

However, we were able to validate the rPAM score in a large allo-HCT cohort of patients with heterogeneous hematological diseases treated with different conditioning regimens. Until now, the rPAM score is not commonly incorporated in the pre-transplant risk score measurement. The results of our study may stimulate the clinicians to use the rPAM score in combination to other well-established pretransplant scores such as the EMBT and HCT-CI score, to receive additional information on the potential risk for impaired outcome after allo-HCT. Since novel therapeutic approaches become available in hematology, the balance between benefit of allo-HCT and risks becomes increasingly important.

In conclusion, in our real-world cohort with extended follow-up, the rPAM score was an independent predictor of the OS, in particular of the NRM, in patients undergoing allo-HCT for different hematologic disorders.

**AUTHOR CONTRIBUTIONS**

NF, JRP and MK designed research, performed research, analyzed data and wrote the manuscript. JAR analyzed data and wrote the manuscript. HB contributed to data extraction and reviewed the manuscript. DS, MM, DH, MT, JPH analyzed data and reviewed the manuscript.

**DISCLOSURES**

The authors have no conflicts of interest to disclose.

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