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Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for Advanced Hodgkin Lymphoma in the Modern Era

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Abstract

The international prognostic score (IPS-7) is the most commonly used risk stratification tool for advanced Hodgkin lymphoma (HL), however recent studies suggest the IPS-7 is less discriminating due to improved outcomes with contemporary therapy. We evaluated the seven variables for IPS-7 recorded at study entry for 854 patients enrolled on E2496. Univariate and multivariate Cox models were used to assess their prognostic ability for freedom from progression (FFP) and overall survival (OS). The IPS-7 remained prognostic however its prognostic range has narrowed. On multivariate analysis 2 factors (age, stage) remained significant for FFP and 3 factors (age, stage, hemoglobin) for OS. An alternative prognostic index, the IPS-3, was constructed using age, stage, and hemoglobin, which provided 4 distinct risk groups [FFP ($p=0.0001$) and OS ($p<0.0001$)]. IPS-3 outperformed the IPS-7 on risk prediction for both FFP and OS by model fit and discrimination criteria. Using reclassification calibration 18% of IPS-7 low risk patients were re-classified as intermediate risk and 13% of IPS-7 intermediate risk patients as low risk. For patients with advanced HL, the IPS-3 may provide a simpler and more accurate framework for risk assessment in the modern era. Validation of these findings in other large data sets is planned.

Keywords

Hodgkin lymphoma; IPS; prognostic score; ABVD; Stanford V

Introduction

Hodgkin lymphoma (HL) is the most common lymphoid neoplasm in young patients, with a median age at diagnosis of 38 years, and approximately 40% of patients under age 35 Cancer facts and figures 2013. Atlanta GA: American Cancer Society, 2013.. In the current era, more than 75% of patients are cured with contemporary frontline therapy (Engert, *et al* 2012, Federico, *et al* 2009b, Gordon, *et al* 2013, Viviani, *et al* 2011). Despite this success,

patients with primary refractory disease or those who relapse after salvage strategies continue to have poor outcomes (Arai, *et al* 2013). The most widely utilized clinical index to assign upfront risk in HL is the International Prognostic Score (IPS), a retrospectively developed clinical model with a primary endpoint of freedom from progression (FFP) (Hasenclever and Diehl 1998). The IPS was constructed in 1998 based on outcomes from approximately 4,600 patients treated on protocols for advanced stage HL prior to 1992. Complete data were available on 1,600 of these patients, and were used to fit the final Cox model. While the majority of patients had advanced stage (45% stage III, 43% stage IV), approximately 13% of patients were classified as stage I or II, and 22% had bulky mediastinal presentation. Therapy was variable and while the majority of patients (75%) were treated with at least 4 cycles of doxorubicin containing chemotherapy, 20% received mechlorethamine, oncovin, procarbazine, and prednisone (MOPP) or a similar regimen, which have been proved to be inferior to ABVD or other doxorubicin-containing regimens. Seven clinical parameters determined to be significant on multivariate analysis were independently associated with adverse clinical outcome; male sex, age >45 years, stage IV disease, hemoglobin <10.5g/dl, white blood count (wbc) $\geq 15 \times 10^9$/L, lymphocyte count < 0.6×10^9/L or <8% of total WBC, and albumin < 40g/L. On the basis of the number of factors present at diagnosis the IPS identified 6 subgroups of patients with 5 year FFP ranging from 42% to 84%, and overall survival (OS) of 56%-89% (Hasenclever and Diehl 1998).

Since the development of the IPS, there have been considerable improvements in therapy and supportive care in both the front line and relapsed setting, resulting in significant improvement in outcome (Eich, *et al* 2010, Engert, *et al* 2010, Straus, *et al* 2004, Younes, *et al* 2012). Additionally newer imaging modalities i.e. PET/CT may allow for more precise staging and response assessment during treatment (Barrington, *et al* 2014, Biggi, *et al* 2013, Cheson, *et al* 2014, Gallamini, *et al* 2007, Hutchings, *et al* 2005).

Although the IPS continues to be widely used, its utility for patients treated with contemporary regimens has been challenged. A retrospective analysis from British Columbia Cancer Agency (BCCA) in patients treated between 1980 and 2010 with ABVD, or an equivalent regimen reported an improvement in outcome and a diminished prognostic range of the IPS-7 with FFP ranging from 62% to 88% and OS ranging from 67% to 98% (Moccia, *et al* 2012). To assess the utility of the individual IPS-7 factors in the contemporary era we analyzed data from a prospective phase III randomized trial ECOG 2496, a study that evaluated ABVD versus Stanford V in advanced HL (Gordon, *et al* 2013).

Patients and Methods

Patient Population

Between 1996 and 2006, 854 patients were enrolled on the North American Intergroup trial E2496, a Randomized Phase III Trial of ABVD versus Stanford V in Locally Extensive and Advanced Stage Hodgkin Lymphoma (Gordon, *et al* 2013). As IPS was one of the stratification factors used in the trial, all 7 IPS variables were recorded at the time of study entry.

Statistical Analysis

FFP was defined as the time from study entry to disease progression or relapse; deaths that occurred during remission that were not preceded by disease progression/relapse were censored. OS was defined as the time from study entry to death from any cause. The Kaplan-Meier method and Cox proportional regression model were used to estimate failure rates, hazard ratios (HRs), and 95% CIs. Log-rank test was used to compare the survival distributions between groups Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 53: 457-481, 1958., Cox, D. R.; Oakes, D. (1984). Analysis of Survival Data. New York: Chapman & Hall. ISBN 041224490X.

The prognostic ability of individual IPS factors was evaluated for FFP and OS in both univariate and multivariable Cox regression models. A new 3-factor prognostic score (IPS-3) was constructed utilizing factors that were significant in multivariate Cox models. Possible alternative cut-off points for the 3 selected factors were evaluated using Chi-square statistics. FFP and OS curves were used to classify patients into 3 risk groups low, intermediate, and high based on number of risk factors: 0-2, 3-4 and ≥5 factors for IPS-7; 0, 1-2 and 3 factors for IPS-3, respectively. The prognostic performance of IPS-7 and IPS-3 was evaluated using the global model fit criteria Akaike information criterion (AIC), concordance probability estimate (CPE), and time-dependent AUC (area under ROC curve) for both FFP and OS Akaike, H. (1974) A new look at the statistical model identification. IEEE Transactions on Automatic Control, 19, 716–723, Gonen, M. & Heller, G. (2005) Concordance probability and discriminative power of proportional hazards regression. Biometrika, 92, 965–970. Lower AIC, higher CPE, and/or higher AUC indicated better concordance. The reclassification calibration method was used to cross-tabulate all risk groups by IPS-7 and IPS-3 (Cook and Ridker 2009, Heagerty and Zheng 2005). Specifically, for cases that were re-classified to different risk group by IPS-3, the observed FFP and OS estimates were compared to survival rates predicted by IPS-7 and IPS-3 respectively. The primary analysis includes all randomized patients. An additional subset analysis was performed on patients with advanced stage III-IV. The analysis was performed using SAS 9.3 and R 3.0.3.

Results

Patient Characteristics

Patient characteristics comparing E2496, original IPS report and the BCCA cohort are shown in Table S1. In E2496 most patients (62%) had stage III or IV disease and the remainder (37%) bulky stage I or II disease.

Evaluation of Outcome for E2496 Patients by IPS-7

As previously reported, there were no significant differences between the two arms (ABVD versus Stanford V) for failure free survival (FFS) and OS at a median follow-up of 6.4 years (Gordon, *et al* 2013).

The IPS-7 remained prognostic for FFP (p=0.012) and OS (p<.0001) as shown in Figure 1a and 1b, however, the separation among IPS-7 groups has narrowed. For patients in both the

highest and lowest risk groups, Kaplan-Meier curves of FFP and OS largely overlap. Risk prediction by IPS-7 in the E2496 cohort is similar to the BCC report, but differs from the original report by Hasenclever (Table S2).

Significance of Individual Seven Factors Used in IPS-7

Table 1 summarizes the results of univariate and multivariate Cox regression assessing the prognostic ability of the 7 individual IPS factors for both FFP and OS. On multivariate analysis, two factors (hemoglobin level and stage) were significant in predicting FFP and three factors (age, hemoglobin level, and stage) were significant for OS. Lymphocyte count was marginally significant for FFP prediction in univariate analysis (p=0.08), but lost its prognostic effect (p=0.29) when put together in the model adjusting for hemoglobin level and stage. A similar observation was seen for albumin in predicting OS (p=0.04 in univariate analysis and 0.31 in multivariate analysis).

Evaluation of a Simpler 3 Factor Prognostic Score (IPS-3)

An alternative prognostic score (IPS-3) was constructed utilizing the variables that remained significant for predicting FFP or OS on multivariate analysis (Table 1): age≥45 years, hemoglobin<10.5g/dl, and stage IV. More than half (56%) of the patients had none of these risk factors, 32% of patients had 1 risk factor, and 10% 2 risk factors. Only 3% (23 patients) had all 3 risk factors. The IPS-3 was significant for both FFP (p=0.0001) and OS (p<.0001) and separated patients into 4 distinct risk groups (Figures 1c and 1d). The five-year FFP by IPS-3 was 83%, 74%, 68%, and 63% and OS 95%, 85%, 75%, and 52% for patients with 0, 1, 2, and 3 risk factors, respectively.

We also explored different cut-off values of age, stage, and hemoglobin: age 50 versus 55 versus 60, stage III/IV versus stage I/II, and hemoglobin of < 10 g/dl versus <9.5 g/dl. Chi-square statistics and hazard ratio associated with different cut-off values are displayed in Table S2. The largest Chi-square statistics selected to refine the IPS-3 were age>55, stage III/IV, and hemoglobin <10.5 g/dl. The results comparing the two models (original versus refined IPS-3) did not show meaningful difference to support the alternative cut-offs. There were very little differences in CPE between the two models (0.58 versus 0.60 for FFP, and 0.65 versus 0.65 for OS). Therefore for further analysis the original cut-off points were used in IPS-3.

Subset Analysis in Patients with Advanced Stage Diseases

To assess the utility of the IPS-7 and the IPS-3 in patients restricted to advanced disease (stage III-IV) we performed an additional subset analysis. Among the 529 (62%) patients in this category, IPS-7 was not significant for FFP [p=0.15, Figure S1 (a)], but remained highly prognostic for OS [p<=0.0001; Figure S1 (b)]. For IPS-3 there is separation for FFP curves [Figure S1, (c)], however the difference is not statistically significant (p=0.11). IPS-3 also remained highly prognostic for OS [p<=0.0001; Figure S1 (d)].

Comparison of IPS-3 to IPS-7

The time-dependent AUC ranked IPS-3 higher than IPS-7 at all times for both FFP and OS (Figure 2a and 2b). IPS-3 was also ranked higher than IPS-7 using the global fit

discriminatory measure (CPE), with 0.58 versus 0.55 for FFP, and 0.65 versus 0.59 for OS. These results suggest a better concordance between the observed data and IPS-3. Lower AIC was seen for IPS-3 than for IPS-7 (2375 versus 2381 for FFP, and 1313 versus 1336 for OS) again indicating better model fit with IPS-3 for both FFP and OS.

We also compared IPS-3 to IPS-7 using reclassification calibration methods. A total of 238 (28%) patients were reclassified to different risk categories by IPS-3 vs IPS-7 (Table 2). Among the IPS-7 low risk patients, 153 (18%) were reclassified as intermediate risk by IPS-3. Both FFP and OS were closer to the predicted survival rates made by IPS-3 than by IPS-7, suggesting that IPS-3 was more accurate for the reclassified 153 patients [Figure 3 (a1, a2)]. Similarly the IPS-3 reclassified 54 (13%) of IPS -7 intermediate risk patients as low risk [Figure 3 (b1, b2)], with FFS and OS curves closer to the predicted survival rates made by IPS-3 than by IPS-7. A very small number (n=28, 3%) of patients were reclassified from IPS-7 high risk to IPS-3 intermediate risk. For this latter group IPS-7 was a better predictor of FFP than IPS-3, however there was no substantial difference in predicting OS, [Figure 3 (c1,c2)].

Discussion

Our analysis of data from E2496 shows that the IPS-7 remains prognostic in the contemporary era, however the magnitude of the differences for both FFP and OS for the lowest and highest risk patients have narrowed, and are consistent with the findings from the BCCA (Moccia, *et al* 2012). In our dataset, only 2 of the original 7 factors used in the IPS-7 remain significant for FFP (age and stage), and 3 factors for OS (age, stage, and hemoglobin). Based on this, a simpler prognostic score the IPS-3 was constructed that identified 4 distinct risk groups based on 0,1,2, or 3 risk factors, which provided risk-stratification for both FFP ($p=0.0001$) and OS ($p<0.0001$). As compared to IPS-7, better global prognostic performance of IPS-3 was suggested by model fit and discrimination criteria. In addition, IPS-3 reclassified 18% of IPS-7 low risk patients as intermediate risk, and 13% of IPS-7 intermediate risk patients as low risk, with observed FFP and OS rate estimates among reclassified patients closer to those predicted by the corresponding IPS-3 category. In our data set, the number of patients in the highest risk group were too few to draw any valid conclusions.

Our study population differs from original IPS-7 report with respect to stage at diagnosis. In the latter study patients with early stage high-risk disease (stages I, II) comprised 13% of the patient population, compared to 37% high-risk stage I and II patients in E2496. Thus to evaluate whether this discrepancy skewed outcomes towards more favorable outcomes with IPS-3 we performed an additional subset analysis restricted to the patients with advanced stage (III-IV) disease. While 4 distinct risk groups were noted the differences were not statistically significant for FFP ($p=0.11$) and remained highly significant for OS ($p<=0.0001$). This was also the case for IPS-7 in our study where differences in FFP were not significant ($p=0.15$). This suggests that patients with a high IPS-3 or IPS-7 at diagnosis may have a worse outcome at relapse than patients with low risk scores.

Therapeutic advances such as the replacement of MOPP chemotherapy with ABVD, use of autologous stem cell transplant at relapse, growth factors to support dose intensity, improved imaging modalities which allow for accurate staging, and increased diagnostic accuracy are some of the key reasons which have contributed to the improvement in patient outcomes in the contemporary era. Yet despite these advances, some patients continue to have extremely poor outcomes. Clinical prognostic factors incorporated within the IPS-7 reflect the interaction of the biologic heterogeneity of HL with treatment. In the original IPS-7 analyses all risk factors were equally weighted. In contrast in the contemporary era, only 3 of these risk factors remained significant and were used to construct IPS-3. Advanced age is well recognized in several studies to be associated with inferior outcome (Engert, *et al* 2005, Evens, *et al* 2013, Landgren, *et al* 2003). Elderly patients are not well represented in the original IPS-7, as only 9% of patients were older than 55 years, with none older than 65 years (Hasenclever and Diehl 1998). By comparison, patients up to age 83 were included in E2496, and 157 (18%) of patients were older than 45 years. Assessing alternative age cutoffs did not appear to improve the prognostic power of the IPS-3, as only a minority (n=12, 1%) of patients were included in the highest risk groups; however using an age cutoff of 50 rather than 45 did appear to potentially discriminate better Additionally age did not appear to affect the total chemotherapy dose received(Evens, *et al* 2013). It is less clear why anemia conferred a higher risk factor for poor OS than other lab parameters such as low albumin, leukopenia, and lymphocytosis. The anemia may have correlated with poor overall fitness and/or poor marrow reserve. It is plausible that anemia may be associated with adverse tumor biology, increased inflammatory cytokine production, and/or macrophage infiltration. Clearly this warrants further investigation.

A potential limitation of our study is that the study patients in E2496 were treated with one of two chemotherapy regimens (ABVD or Stanford V), thus the question of whether the IPS-3 would be applicable to other current dose intense regimens such as escalated BEACOPP, or to novel therapies such as brentuximab vedotin remains to be studied. Another limitation is that despite the overall large sample size of our study, there were very few patients (n=23) who had all 3 IPS-3 risk factors. Finally for the very small number of patients (n=28) of patients who were reclassified from IPS-7 high risk to IPS-3 intermediate risk, the IPS-7 was a better predictor of FFP than IPS-3, however there was no substantial difference in predicting OS. Therefore validation of the IPS-3 in other data sets is definitely required, and modification of the IPS-3 to further refine risk assessment is ongoing. In a largely curable disease it is important to individualize therapy by accurately selecting patients based on risk factors at diagnosis. With the multiplicity of therapeutic options now available for HL, accurate assessment of risk based on outcomes expected with contemporary therapy is more important now than ever before. The distinction of 4 groups by IPS-3 has clinical significance as new therapeutic advances are required for high risk patients, while minimizing therapy to alter the spectrum of long-term therapy related toxicity becomes more important for the low risk patients. As therapeutic strategies evolve these alternative indices are increasingly necessary for patient identification and risk stratification for clinical trials that utilize risk-adapted treatment approaches. There is precedent to refine prognostic scores in other lymphomas as clinical outcomes have evolved with improved therapies as reflected by the revised IPI (R-IPI) in DLBCL, which redistributed the 5 IPI

elements into 3 prognostic groups with 4 year OS ranging from 55% to 94% (Sehn, *et al* 2007), the elderly IPI (E-IPI) which used an age cut off of 70 years rather than the 60 years used in the IPI, and provided additional prognostic discrimination for elderly patients of low and low-intermediate risk (Advani, *et al* 2010), the NCCN IPI in DLBCL(Zhou, *et al* 2014), and the Follicular Lymphoma International Prognostic Index-2 (FLIPI-2) which stratified patients into 3 quartiles based on low risk (0), intermediate risk (1-2), and high risk (Federico, *et al* 2009a).

Advances in of HL biology suggest the significance of the interaction of the HRS cell with its tumor microenvironment for clinical outcomes. Expression of CD68+ and CD163 by tumor-associated macrophages (TAMS) is correlated with inferior PFS and OS (Kamper, *et al* 2011, Steidl, *et al* 2012, Steidl, *et al* 2010, Tan, *et al* 2012). More recently, NanoString digital expression profiling described a 23-gene signature which identified a high risk subset of advanced stage HL patients (Scott, *et al* 2013). Other novel prognostic indicators such as EBV expression and lymphocyte/monocyte ratio have also shown to have prognostic significance (Kanakry, *et al* 2013). Moving forward, a truly comprehensive risk assesment platform must take these biologic features as well as clinical factors into account. Efforts to incorporate these advances into the IPS-3 are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Analysis of 854 advanced HL patients treated on E2496 confirms that the IPS-7 has decreased prognostic discrimination in the contemporary era.
- A simpler prognostic score, the IPS-3, outperformed the IPS-7 and may provide a more accurate framework for risk prediction.

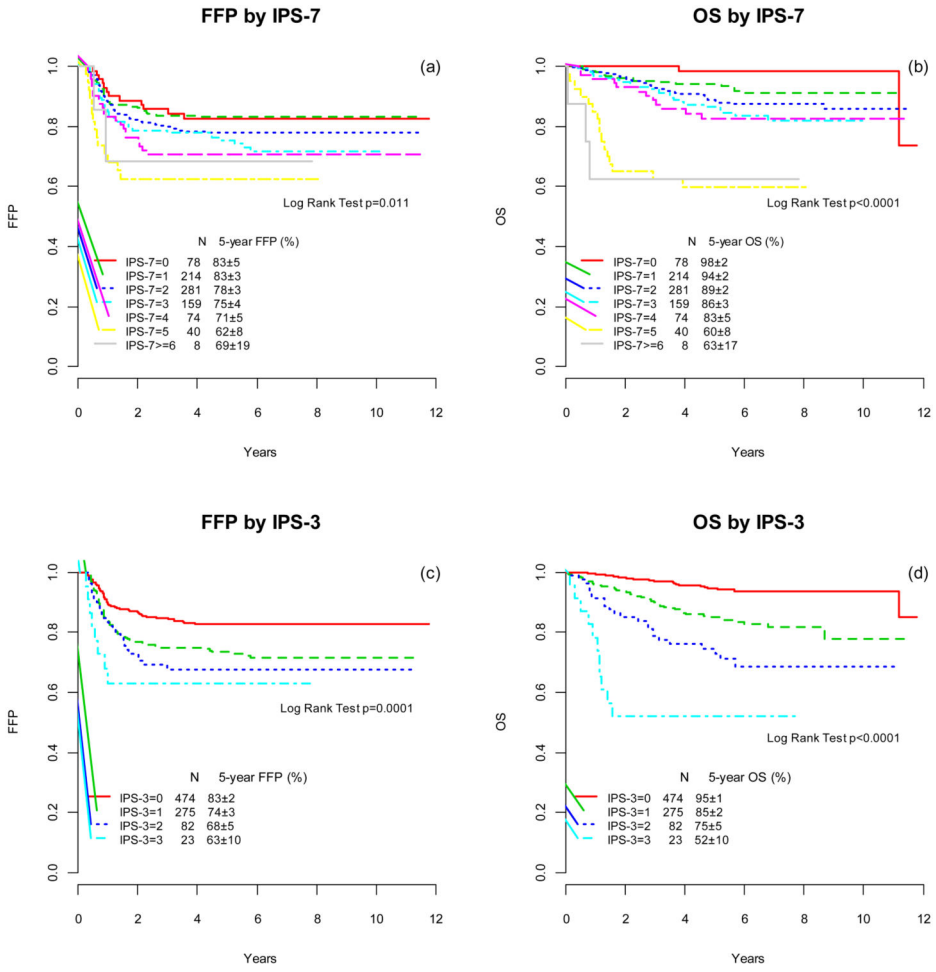

Figure 1.

Freedom from progression (FFP) and overall survival (OS) according to the International Prognostic Score (IPS) factors (a, b) and the simpler prognostic index IPS-3 (c,d)

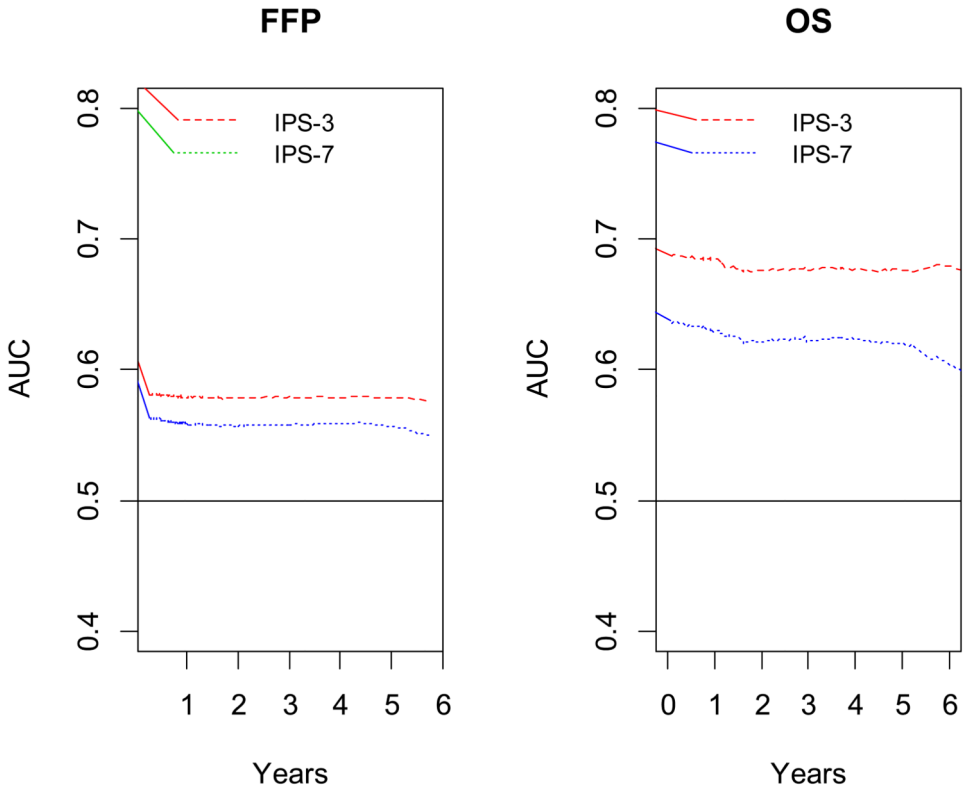

Figure 2.

Time weighted area under the receiver operator characteristics curves (AUC) for freedom-from progression (A) and overall survival (B) according to the International Prognostic Score factors IPS-7 and simpler prognostic index IPS-3.

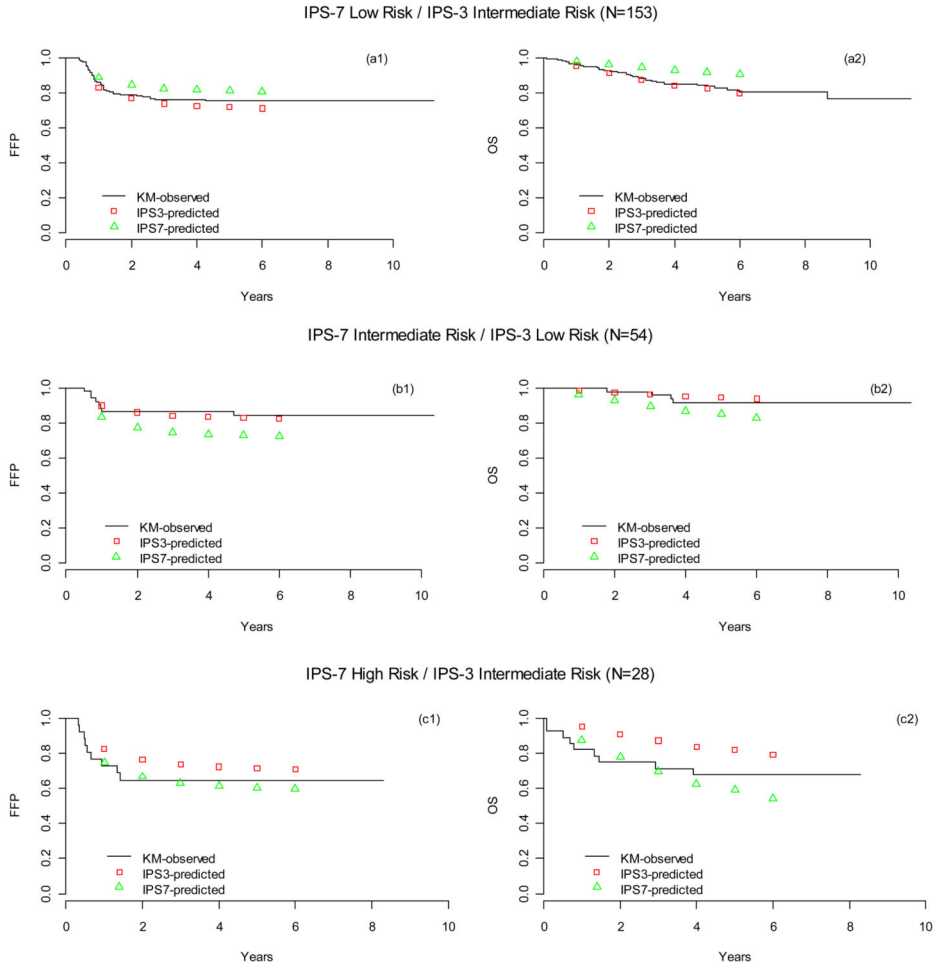

Figure 3. Kaplan-Meier (KM) analysis of observed and predicted (by IPS-7 and IPS-3) FFP and OS for patients whose risk categories were reclassified by IPS-3

N=153 patients low risk by IPS-7 but intermediate risk by IPS-3 (a1, a2); n=54 patients intermediate risk by IPS-7 but low risk by IPS-3 (b1, b2); n=28 patients high risk by IPS-7 but intermediate risk by IPS-3 (c1,c2). The predicted survival rates were produced by univariate Cox models using IPS-3 and IPS-7 as covariates.

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Table 1

Individual IPS factors with FFP and OS by Univariate and Multivariate Analysis

	FFP				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
IPS factor	**HR(95% CI)**	**p-value**	**HR(95% CI)**	**p-value**	**HR(95% CI)**	**p-value**	**HR(95% CI)**	**p-value**
Age≥45 years	1.3 (0.9-1.8)	0.15	1.2 (0.9-1.8)	0.27	4.0 (2.7-5.9)	**<0.0001**	3.7 (2.5-5.5)	**<0.0001**
Albumin<4g/dl	1.0 (0.7-1.4)	0.92	0.8 (0.6-1.1)	0.21	1.6 (1.0-2.5)	**0.04**	1.3 (0.8-2.1)	0.31
WBC≥15,000 mm^3	1.3 (0.9-2.0)	0.20	1.3 (0.8-1.9)	0.28	1.1 (0.7-2.0)	0.64	1.2 (0.7-2.1)	0.52
Hgb<10.5g/dl	1.8 (1.3-2.6)	**0.0003**	1.7 (1.2-2.5)	**0.004**	2.8 (1.9-4.2)	**<0.0001**	2.1 (1.3-3.3)	**0.002**
Lymph count <600 mm^3or <8% of WBC	1.3 (1.0-1.9)	0.08	1.2 (0.8-1.7)	0.29	1.2 (0.7-1.9)	0.48	1.0 (0.6-1.6)	0.91
Male	1.1 (0.8-1.5)	0.55	1.1 (0.8-1.5)	0.55	1.1 (0.8-1.6)	0.57	1.1 (0.7-1.6)	0.68
Stage IV	1.7 (1.3-2.4)	**0.0005**	1.5 (1.1-2.1)	**0.02**	2.3 (1.6-3.4)	**<0.0001**	1.7 (1.1-2.5)	**0.02**

*Factors and numbers in bold indicate significant p-values in the analysis.

Table 2

Reclassification: Number of Patients in Each Risk Category by IPS-7 and IPS-3

		IPS-7			
		Low Risk (0-2)	**Intermediate Risk (3-4)**	**High Risk (5-7)**	**Total**
IPS-3	Low Risk (0)	420	**54**	0	474 (56%)
	Intermediate Risk (1-2)	**153**	176	**28**	357 (42%)
	High Risk (3)	0	**3**	20	23 (3%)
	Total	573 (67%)	233 (27%)	48 (6%)	854

*Numbers in bold indicate patients who were reclassified.