Time for a New, More Inclusive Endpoint for Treatment of Type 1 Hepatorenal Syndrome (HRS-1)? Small Changes in Serum Creatinine (SCr) of >20% Are Equivalent to HRS Reversal (HRSR) in Predicting Survival and Need for Renal Replacement Therapy (RRT) During Treatment of HRS-1 With Terlipressin and Albumin

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◆ Background and Aims

► The generally accepted and clinically applied endpoint for successful treatment of type 1 hepatorenal syndrome (HRS-1) is a fall in serum creatinine (SCr) from ≥2.5 mg/dL to ≤1.5 mg/dL, so called HRS reversal (HRSR)[1]

► Recently, a new classification for acute kidney injury in patients with cirrhosis has been proposed, using the Acute Kidney Injury Network (AKIN) criteria[2]

► The AKIN classification is based on observations that an acute increase in SCr in cirrhotics is associated with a worse prognosis[2]

  – Assesses response to treatment based on regression of AKIN stage

► Based on our previous observation of a correlation of changes in SCr during treatment with survival,[3] we questioned whether small decreases in SCr following treatment would be associated with improved survival and reduced use of renal replacement therapy (RRT) with similar or better predictive values compared with HRSR

◆ Material & Methods

► We analyzed the large, combined data set from our 2 published studies (OT-0401 and REVERSE) evaluating terlipressin in HRS-1[3,4]

► Data were available for 308 patients with well-characterized HRS-1 from the 2 studies

► Data were analyzed for the predictive value of HRSR (20% or 30% improvement in SCr) for survival and the use of RRT. Positive predictive value (PPV), negative predictive value (NPV), accuracy, sensitivity, and specificity were determined using standard definitions

► Receiver operator curves (ROCs) were generated for overall survival by improvement in SCr from baseline to the end of treatment (EOT) and HRSR by improvement in SCr from baseline to EOT

► Youden's index as an estimate of optimal cutoff for the ROCs was derived using the standard formula (Youden index = sensitivity + specificity − 1)
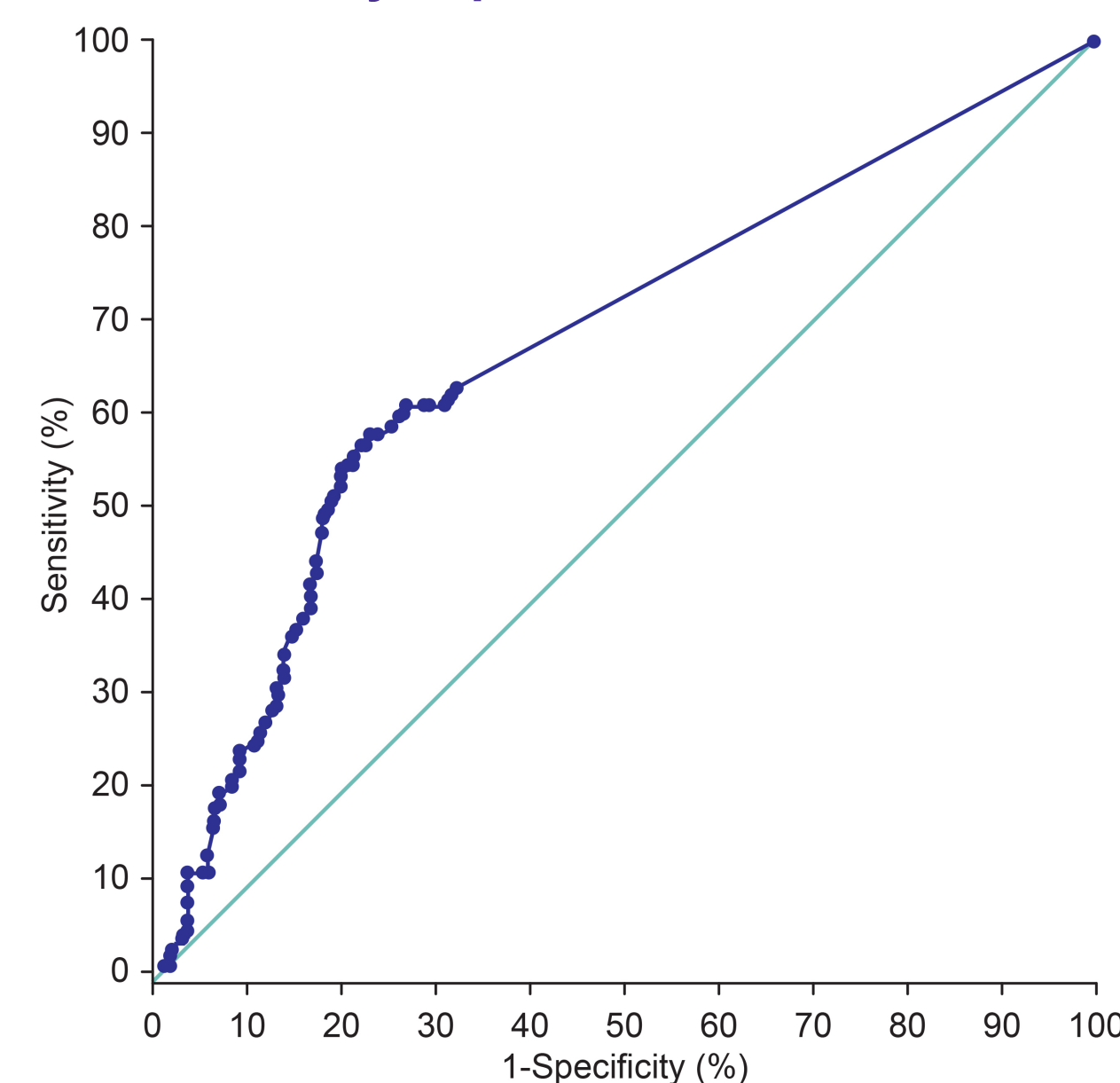
◆ Results

► 64 patients (21%) achieved HRSR and 118 patients (38%) had at least a 20% fall in SCr

► A 20% reduction in SCr gave predictive, sensitivity, and specificity values that were similar to HRSR for survival (**Table 1**); 30% improvement in SCr did not increase accuracy

► For RRT, results were similar (**Table 2**); HRSR was somewhat more accurate in predicting the use of RRT

► HRSR or improvement in SCr reduced the use of RRT from 50–56% to 9–12%

► The number of patients achieving ≥20% improvement in SCr was twice that of those achieving HRSR in these 2 large studies

► The highest values for the Youden index* for overall survival was 0.353, suggesting an optimal cutoff of 15% improvement in SCr from baseline to EOT (**Figure 1**). The highest value of the Youden index for HRSR was 0.896, suggesting an optimal cutoff of 40% improvement in SCr from baseline to EOT (**Figure 2**)

*The Youden index is the vertical distance between the 45-degree line and a point on the ROC. A recommended approach to determine the optimal cutoff is to identify the cutoff with the highest Youden index.

Table 1. Predictive Value of HRSR and SCr Improvement for Survival

	HRSR	≤20% Reduction in SCr	≤30% Reduction in SCr
PPV	76.6	74.6	74.0
NPV	54.1	61.6	57.6
Sensitivity	30.4	54.7	44.1
Specificity	89.9	79.6	83.0
Accuracy	58.8	66.6	62.7

Table 2. Predictive Value of HRSR and SCr Improvement for Use of RRT

	HRSR	≤20% Reduction in SCr	≤30% Reduction in SCr
PPV	7.8	13.6	12.5
NPV	56.6	50.0	53.3
Sensitivity	4.5	14.4	10.8
Specificity	70.1	48.2	57.4
Accuracy	46.4	36.0	40.6

Figure 1. ROC for Overall Survival by Improvement in SCr

Area under the curve=0.673.

Figure 2. ROC for HRSR by Improvement in SCr
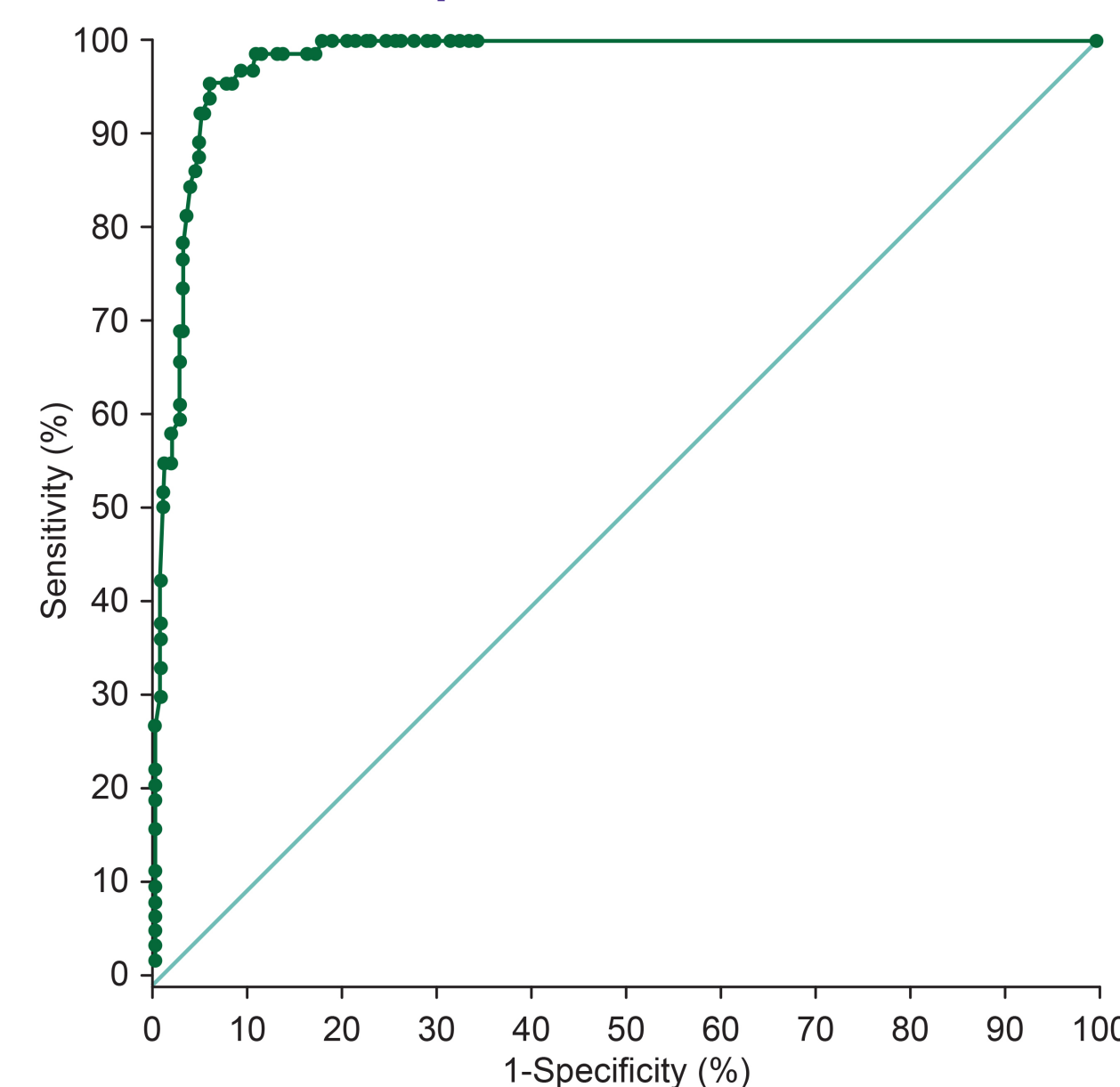
Area under the curve=0.979.

◆ Summary

► Improvement in SCr had similar PPV, NPV, sensitivity, and specificity as HRSR in predicting survival; HRSR and improvement in SCr were similarly accurate in predicting the use of RRT

► The number of patients achieving at least a 20% improvement in SCr was twice that of those achieving HRSR in these 2 large studies

► Small improvements in SCr of 15% are associated with increased survival; an improvement in SCr of 40% was the optimal cutoff for achieving HRSR

CONCLUSIONS

► An improvement in SCr of at least 15–20% is a more inclusive endpoint compared with HRSR, with similar sensitivity and specificity, and thus may be a better assessment of the response to treatment for patients with HRS-1

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