Early Organ Toxicity Post HCT

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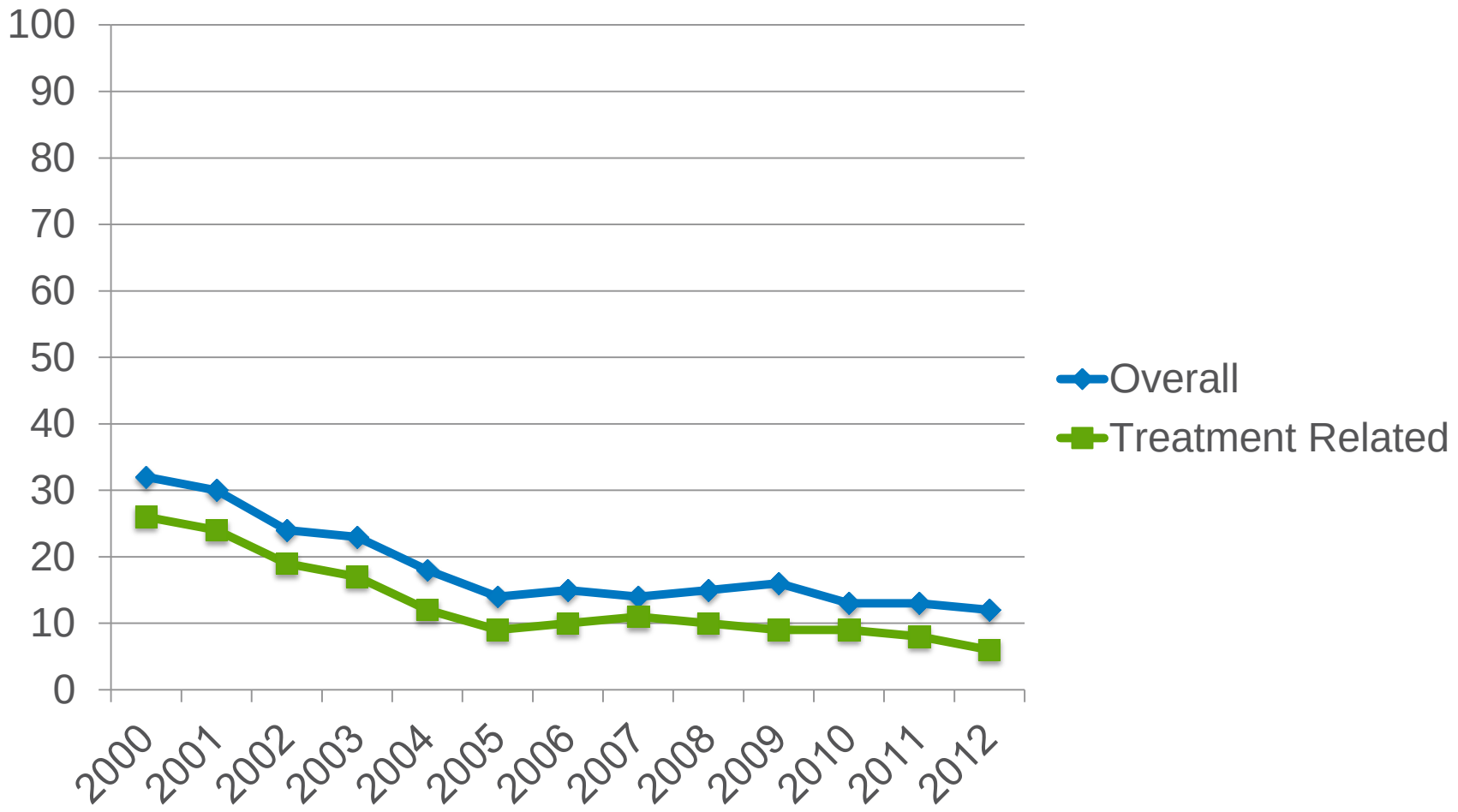
A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

100-Day Mortality by Year of HCT



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Introduction

- Hepatic Veno-Occlusive Disease (VOD), Transplant-Associated Thrombotic Microangiopathy (TA-TMA), and Idiopathic Pneumonia Syndrome (IPS) are phenotypically distinct complications that occur early post HCT and are associated with high mortality rates

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*Richardson PG, et al. BBMT 19 (2013) S88-90
*Laskin BL, et al. Blood 2011. 118: 1452-1462
*Yanik GA, et al. BBMT 20 (2014) 858-864

Introduction

- Endothelial cell injury is a key final pathogenetic finding
- The phenotype is governed by the site of the endothelial cell injury
  - VOD – sinusoidal endothelial cells
  - TA-TMA – kidney
  - IPS - lung

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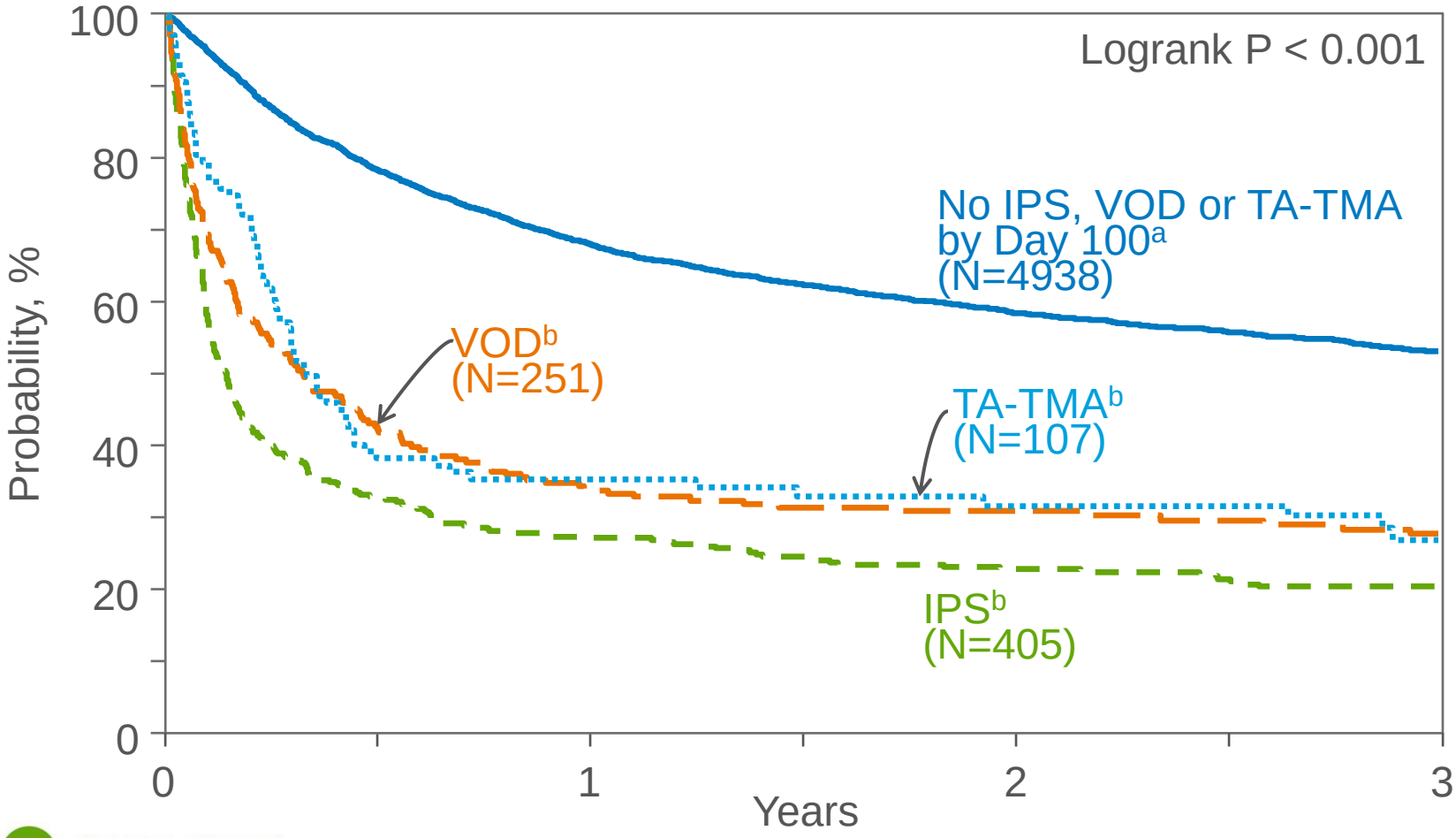
Overall Survival in Patients Who Developed Organ Disorders Within the First 100 Days Post HCT



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[a]Day 0 for survival curve calculations is Day 100 post-HCT

[b]Day 0 for survival curve calculations is date of organ disorder diagnosis

Year of HCT: 2008-2012

VOD

- Conditioning regimen mediated injury to sinusoidal endothelial cells in zone 3 of the hepatic acinus ➔high levels of cytokines (TNF-α and IL-1) and adhesion molecules
- Activation of pro-inflammatory pathways leading to further damage
- Gaps between endothelial cells ➔extravasation of cells ➔compressive narrowing of the sinusoids

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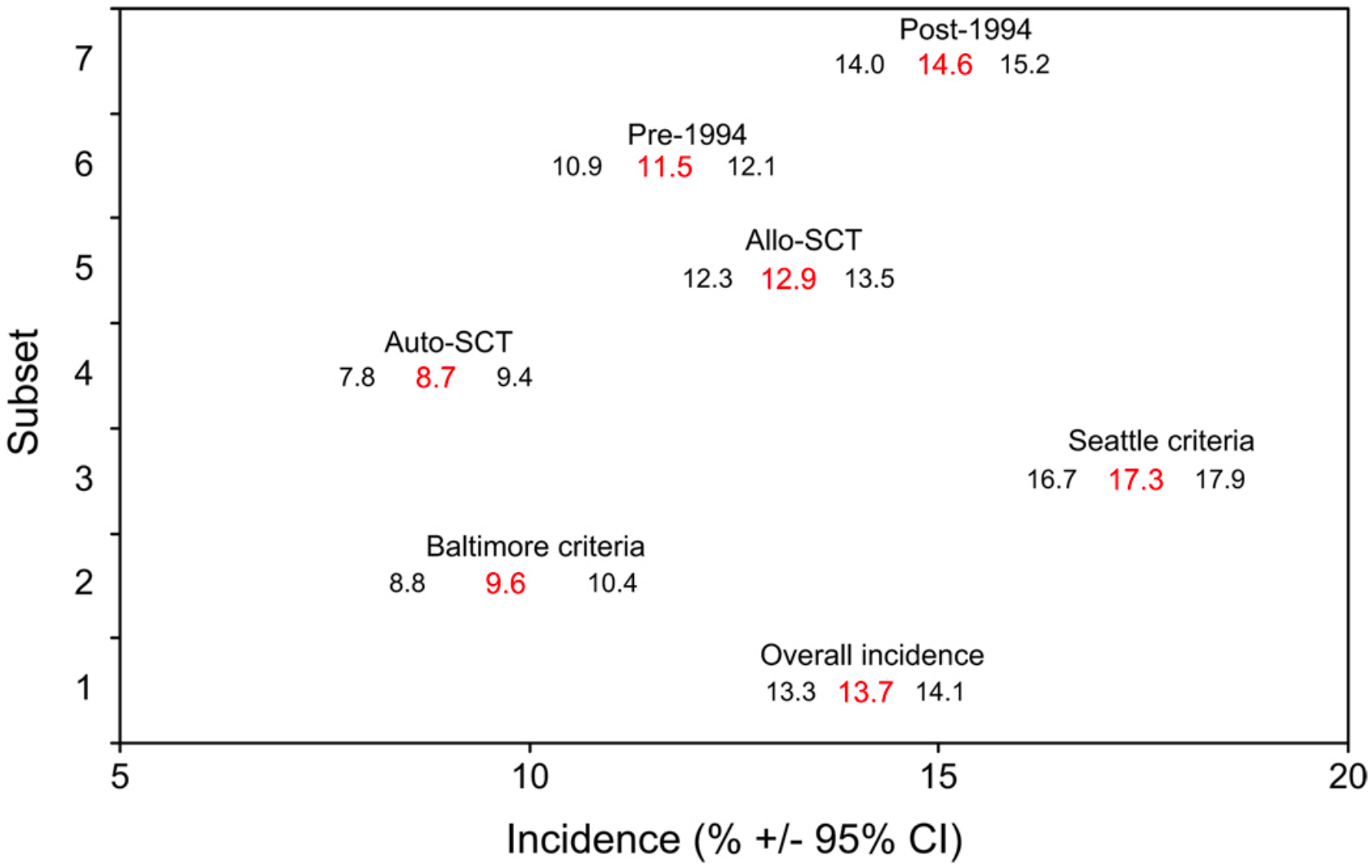
*Dignan FL, et al. BJH 2013. 163: 444-457
*Richardson PG, et al. BBMT 19 (2013) S88-90



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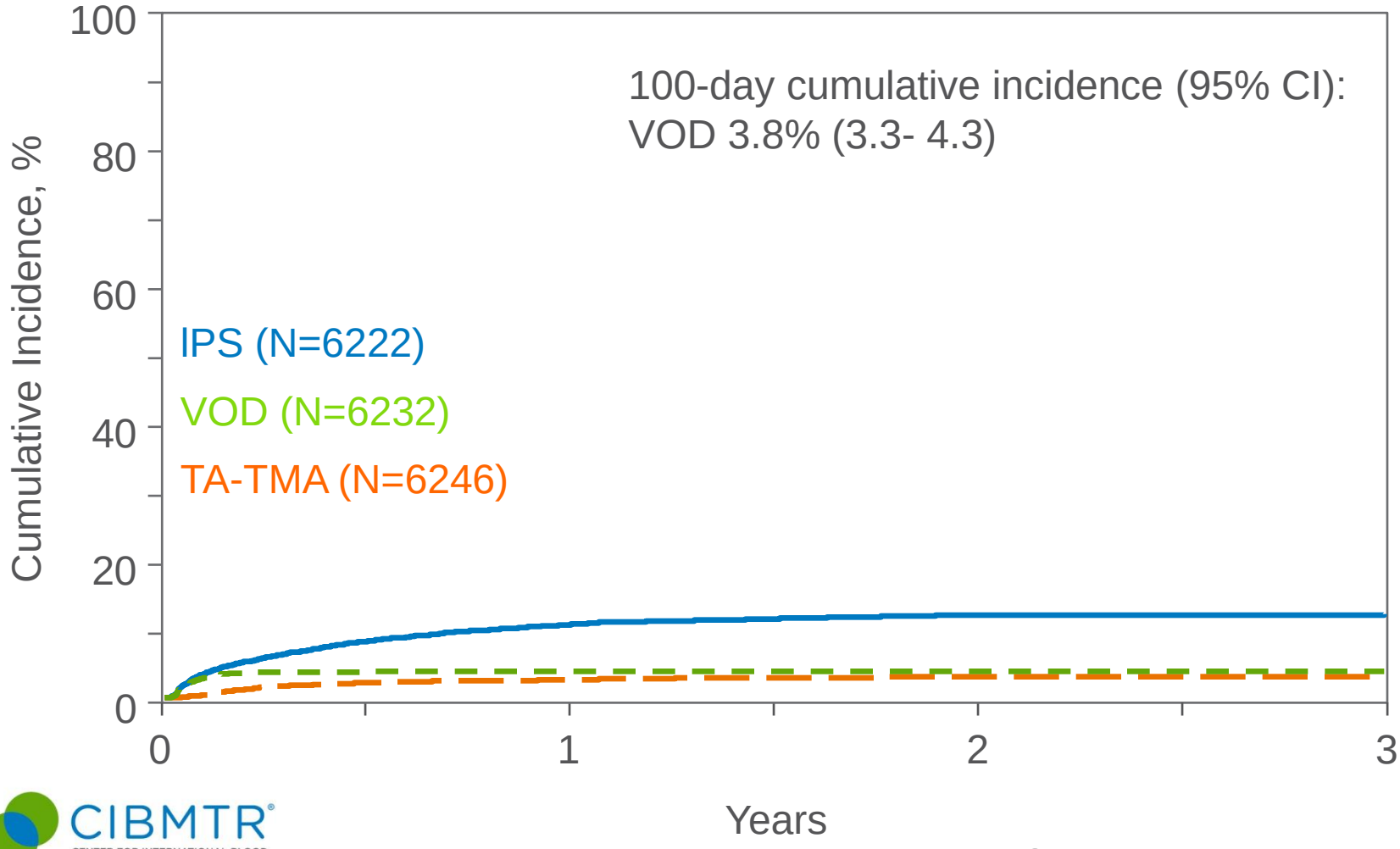
Coppell JA, et al. Biol Blood Marrow Transplant. 2010 Feb;16(2):157-68

Cumulative Incidence of Post-HCT Organ Disease



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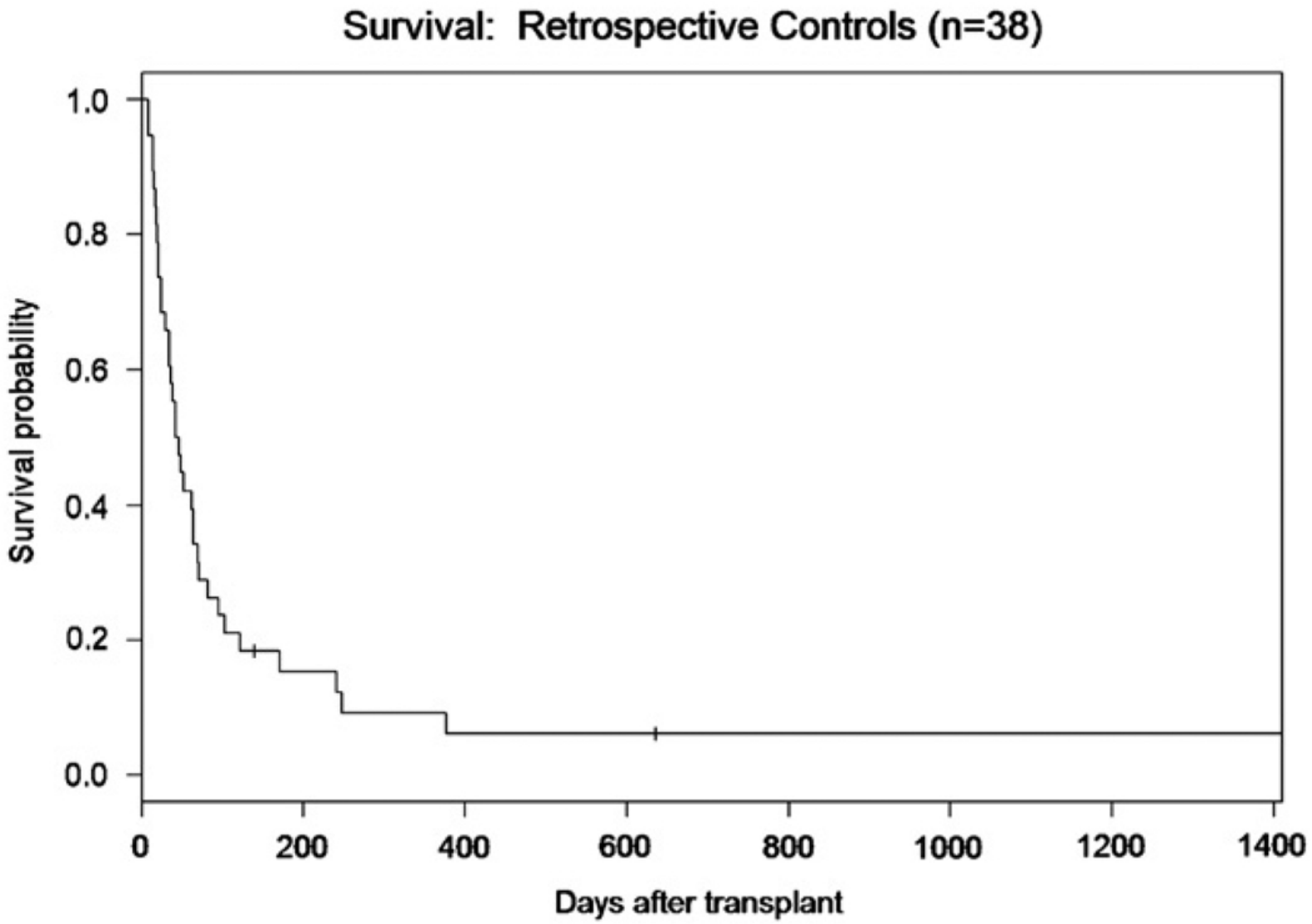
Year of HCT: 2008-2012



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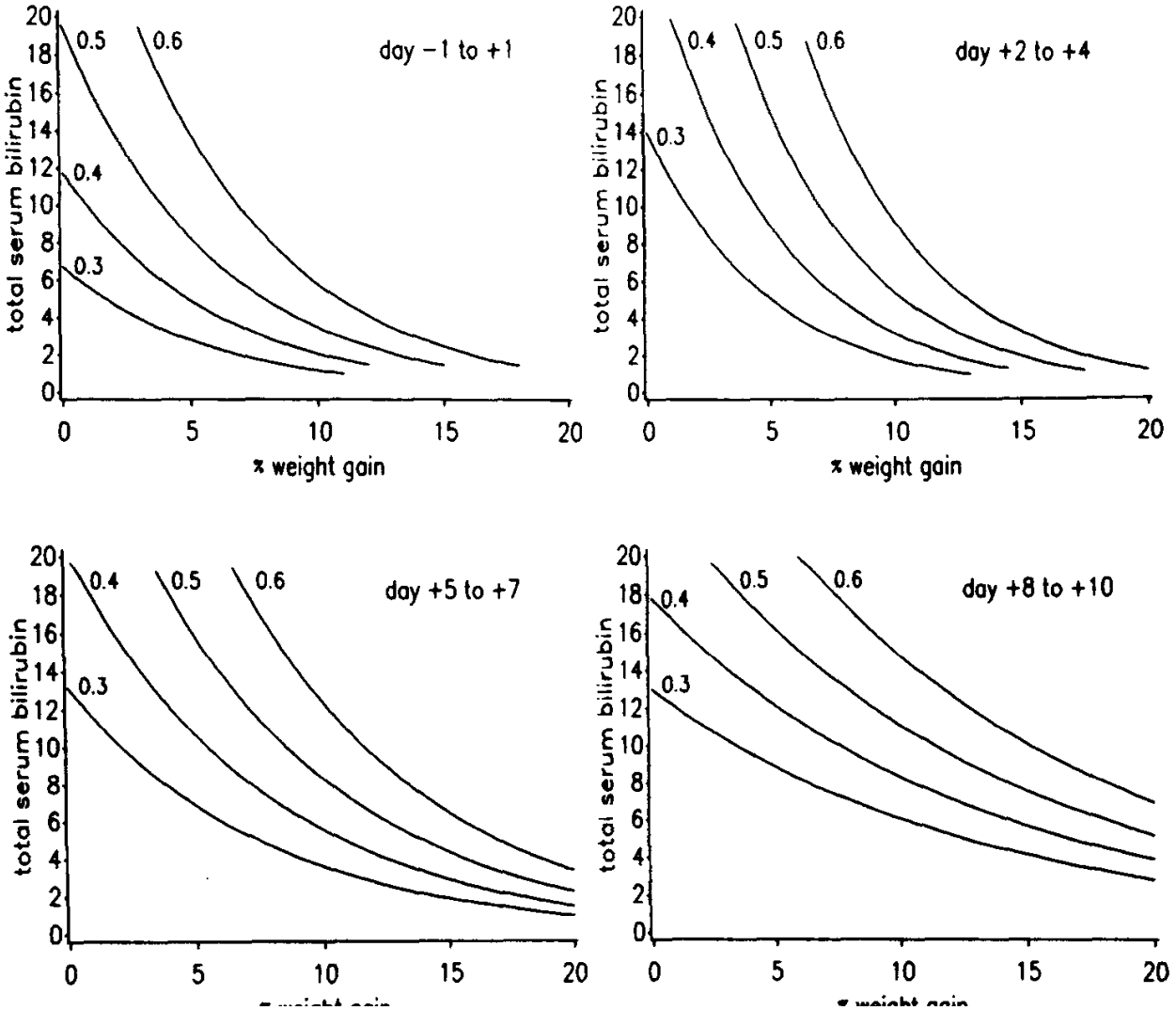

Fig 2. Contour lines estimating probability of developing severe VOD as ≥ 30%, ≥ 40%, ≥ 50%, and ≥ 60% using total serum bilirubin (mg/dL) and percent weight gain above baseline. If the plotted point lies above the probability line, the probability of severe VOD is or exceeds the probability of that line.

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*Bearman SI, et al. JCO 1993. 1729-1736

Risk Factors

- Pre-existing liver disease, including iron overload
- Exposure to gemtuzumab ozogamicin
- Allogeneic HCT vs. autologous HCT
- Second HCTs
- Conditioning regimen intensity
- Busulfan in combination with cyclophosphamide
- Underlying disease
- Age
- Use of sirolimus

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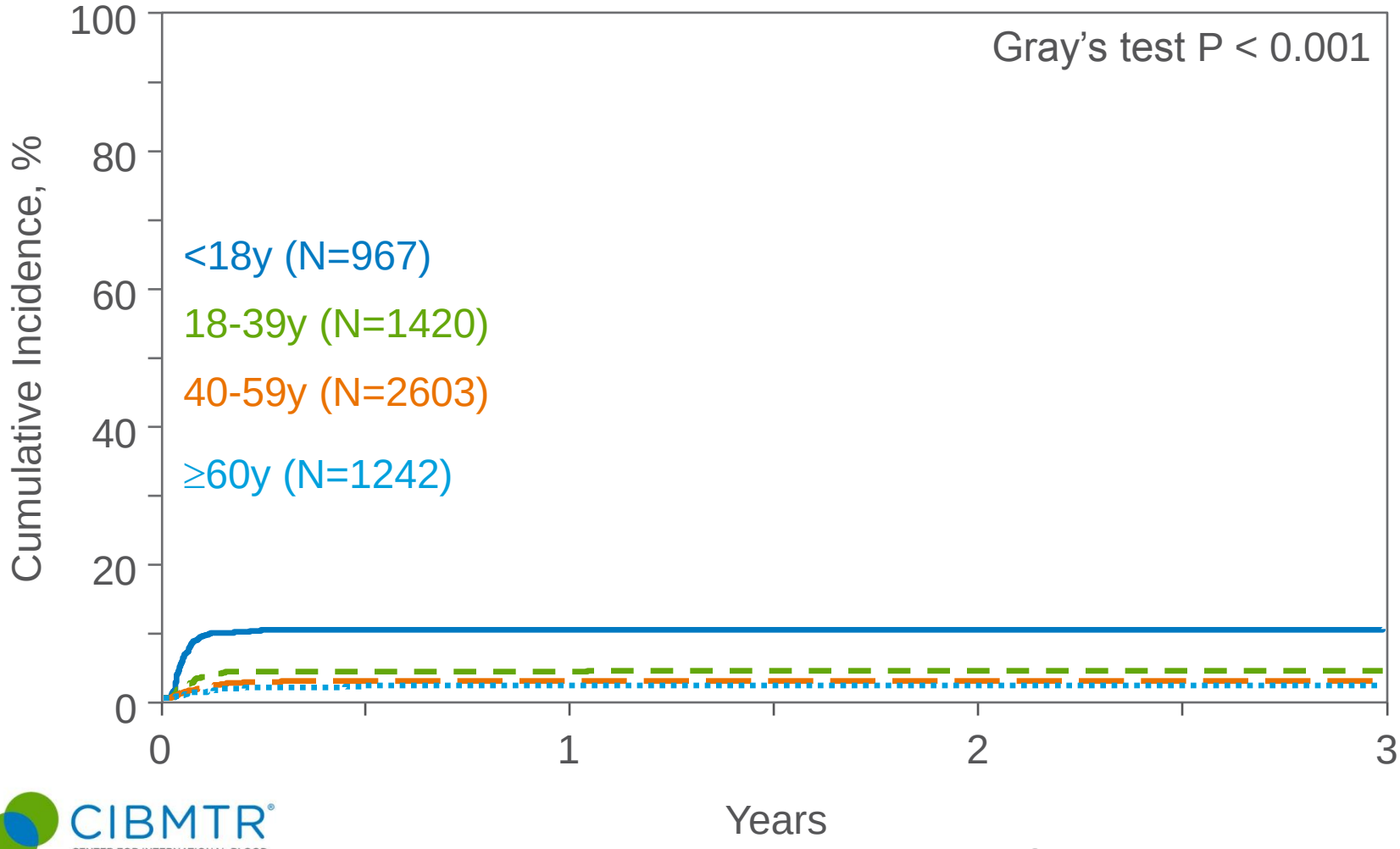
Incidence of Veno-Occlusive Disease by Age at HCT



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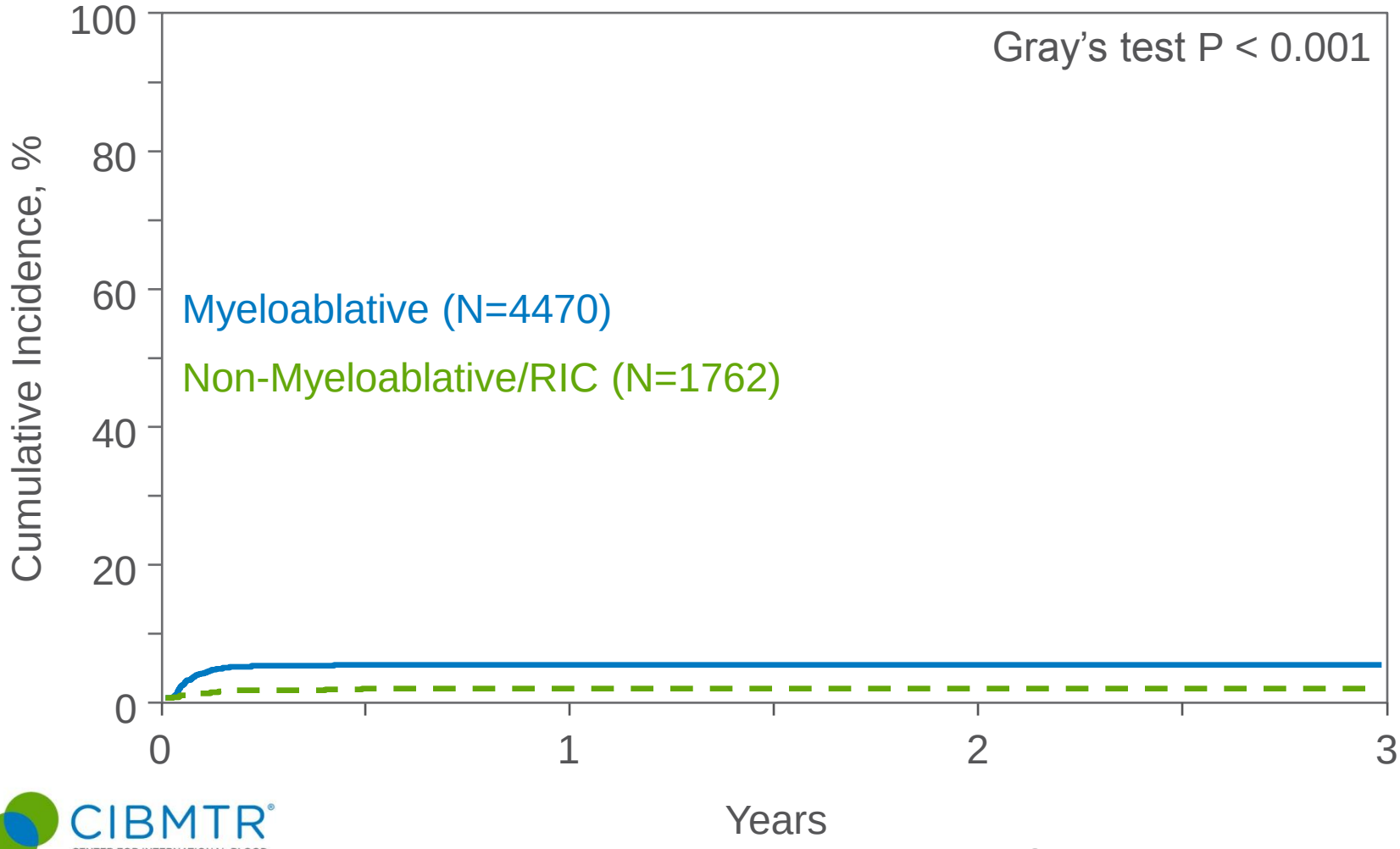
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by Conditioning Regimen Intensity



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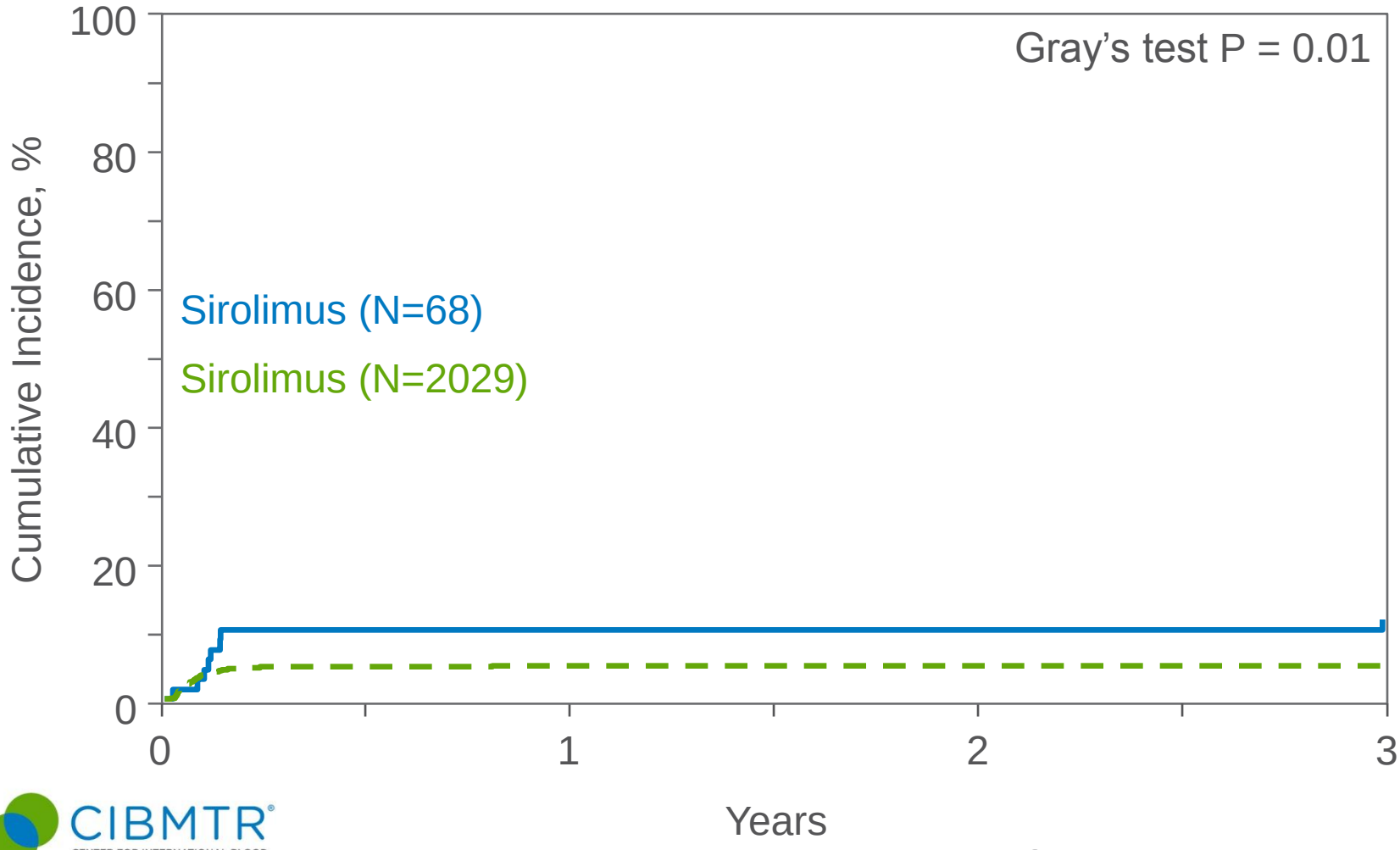
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by Sirolimus Use - Myeloablative Conditioning Regimens with Busulfan Only



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Year of HCT: 2008-2012

Non-significant Factors

- KPS
- Donor type
- Pre-existing liver disease
- TBI
- Busulfan
- Second HCT

Prediction of VOD

- Hypothesis: VOD may be predicted by the measurement of biomarkers of endothelial injury, particularly in patients receiving sirolimus

- **von Willebrand Factor**
- **Thrombomodulin**
- **Soluble Intracellular Adhesion Molecule-1 (ICAM-1)**
- **E-Selectin**

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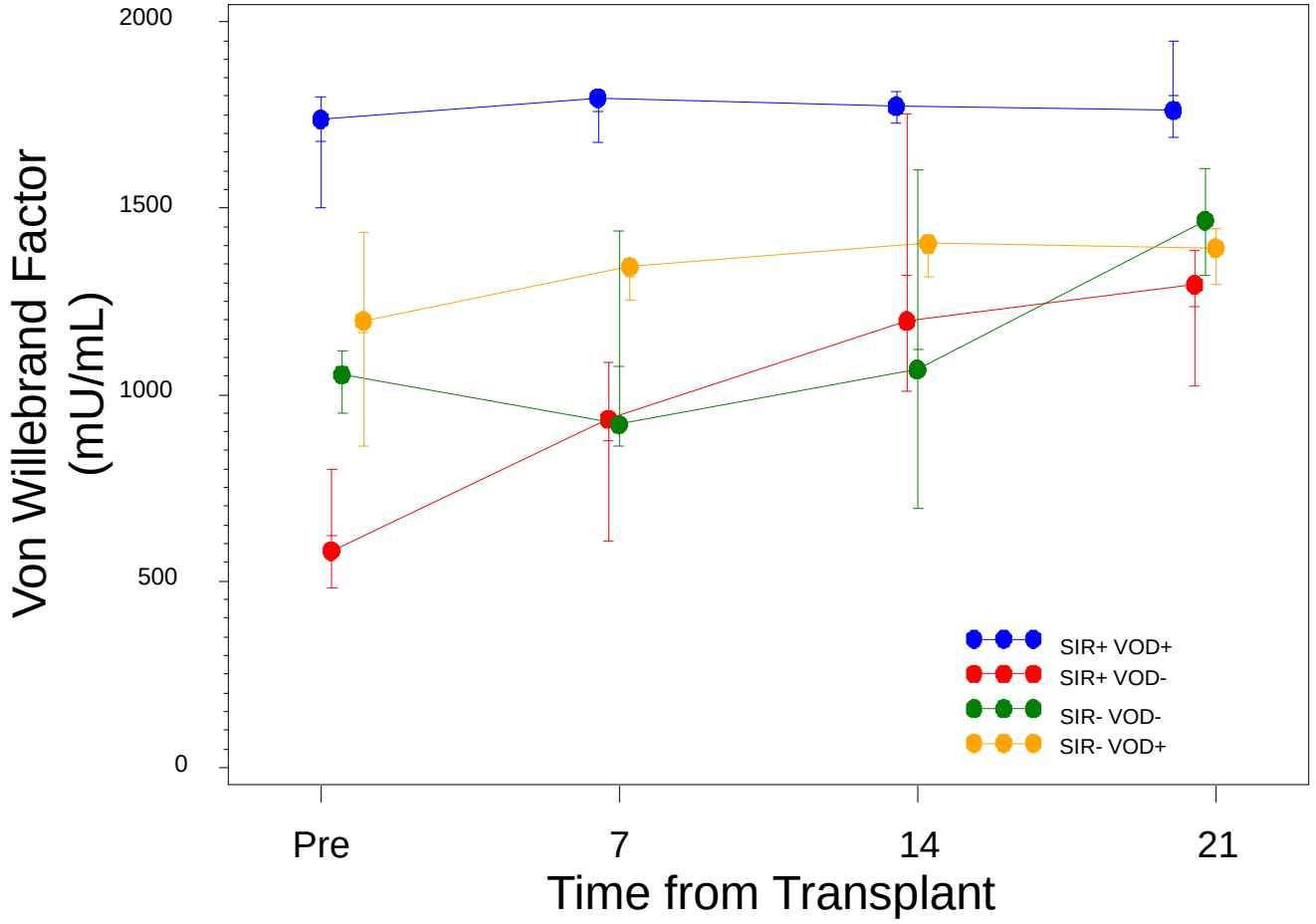
*Cutler C, et al. BBMT 2010. 16 (8): 1180-1185

vWF



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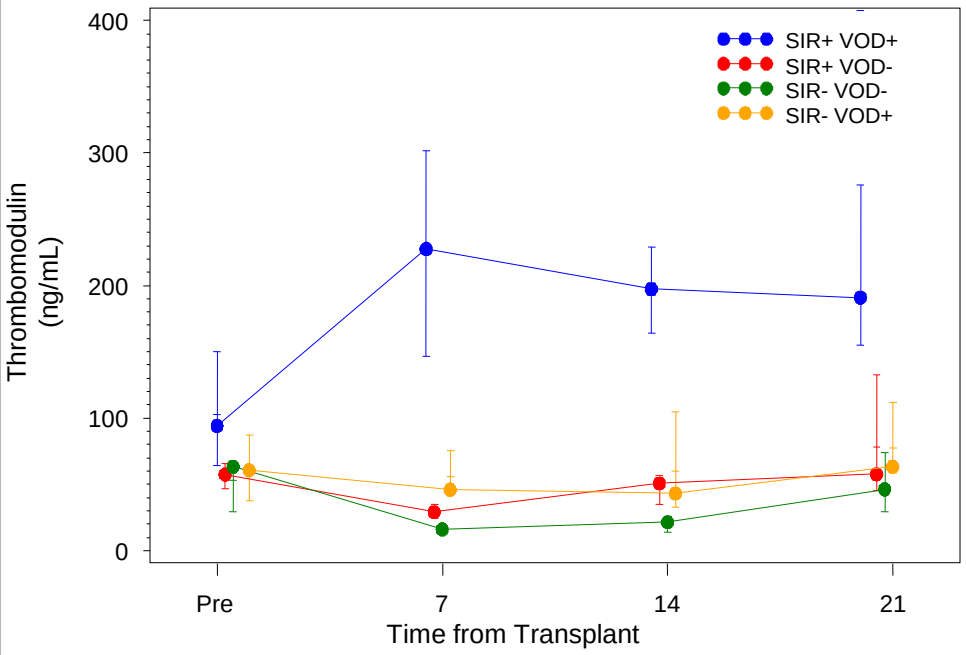
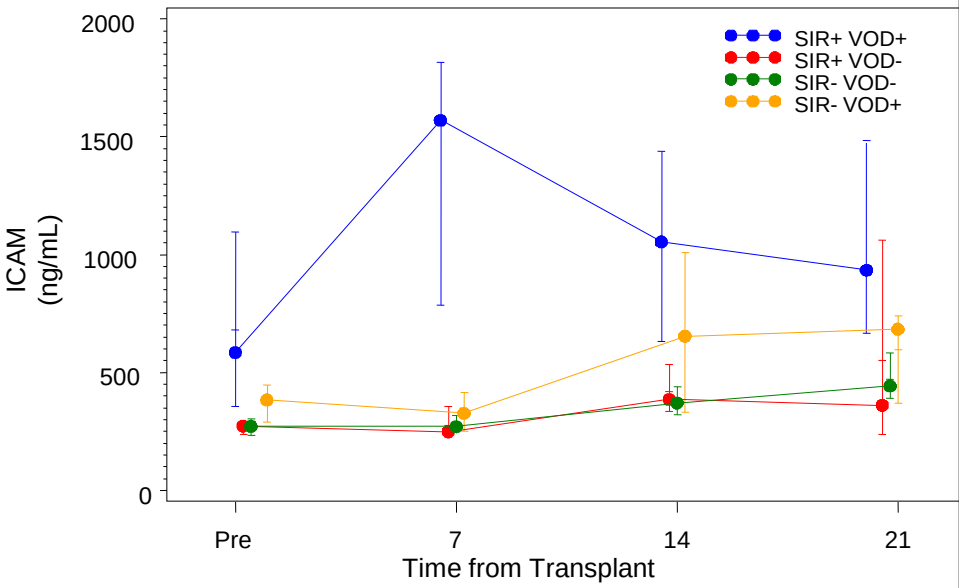
Thrombomodulin / ICAM-1





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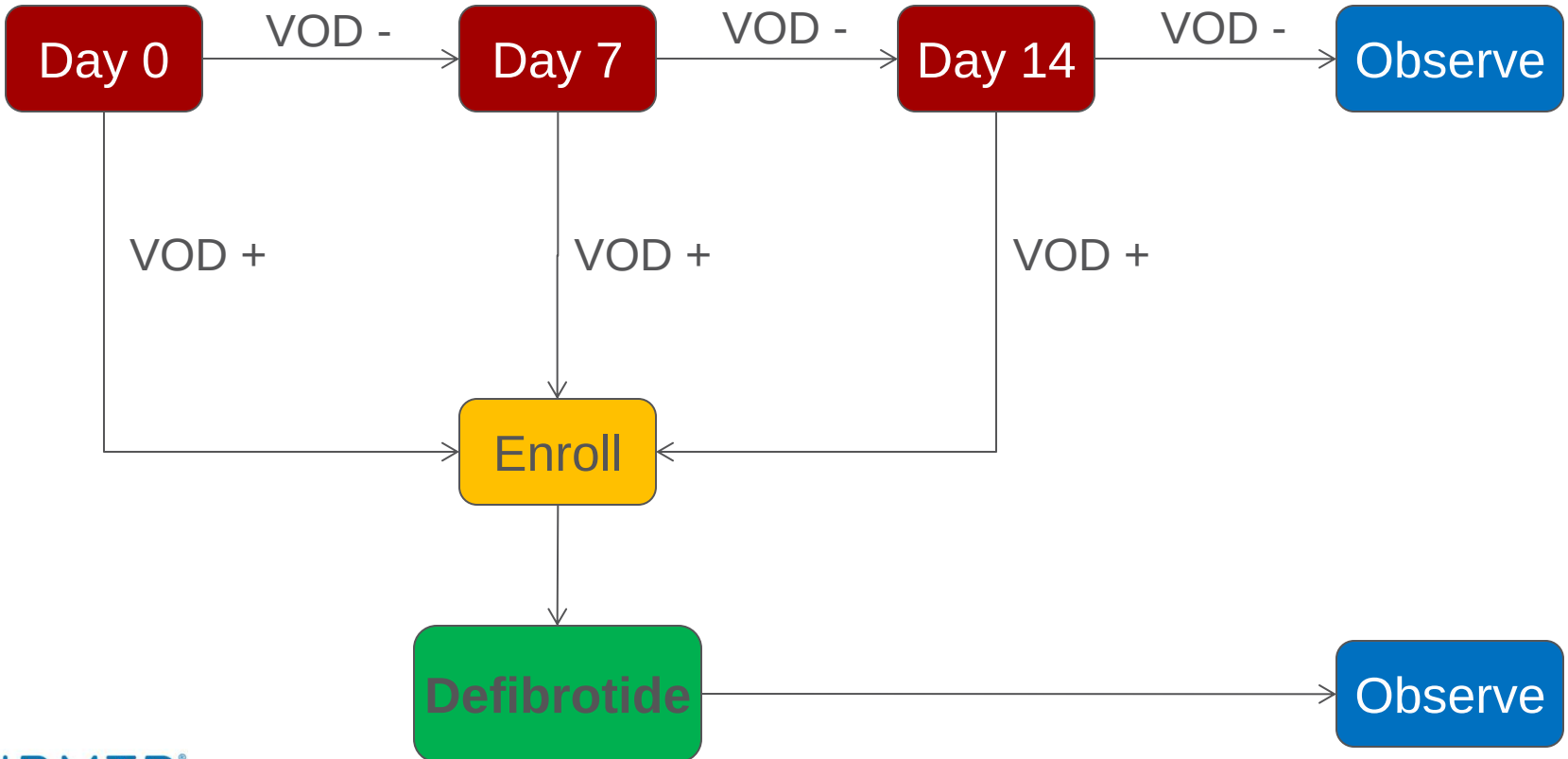
*Cutler C, et al. BBMT 2010. 16 (8): 1180-1185

Pre-Emptive Therapy of VOD



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TA-TMA

- EBMT:

- 2-year incidence of 6.7% (95% CI 4-9)

- median time of onset 44 days (range 13-319) post HCT

- A specific cause of small vessel injury remains unknown
- No association with low ADAMTS13 activity

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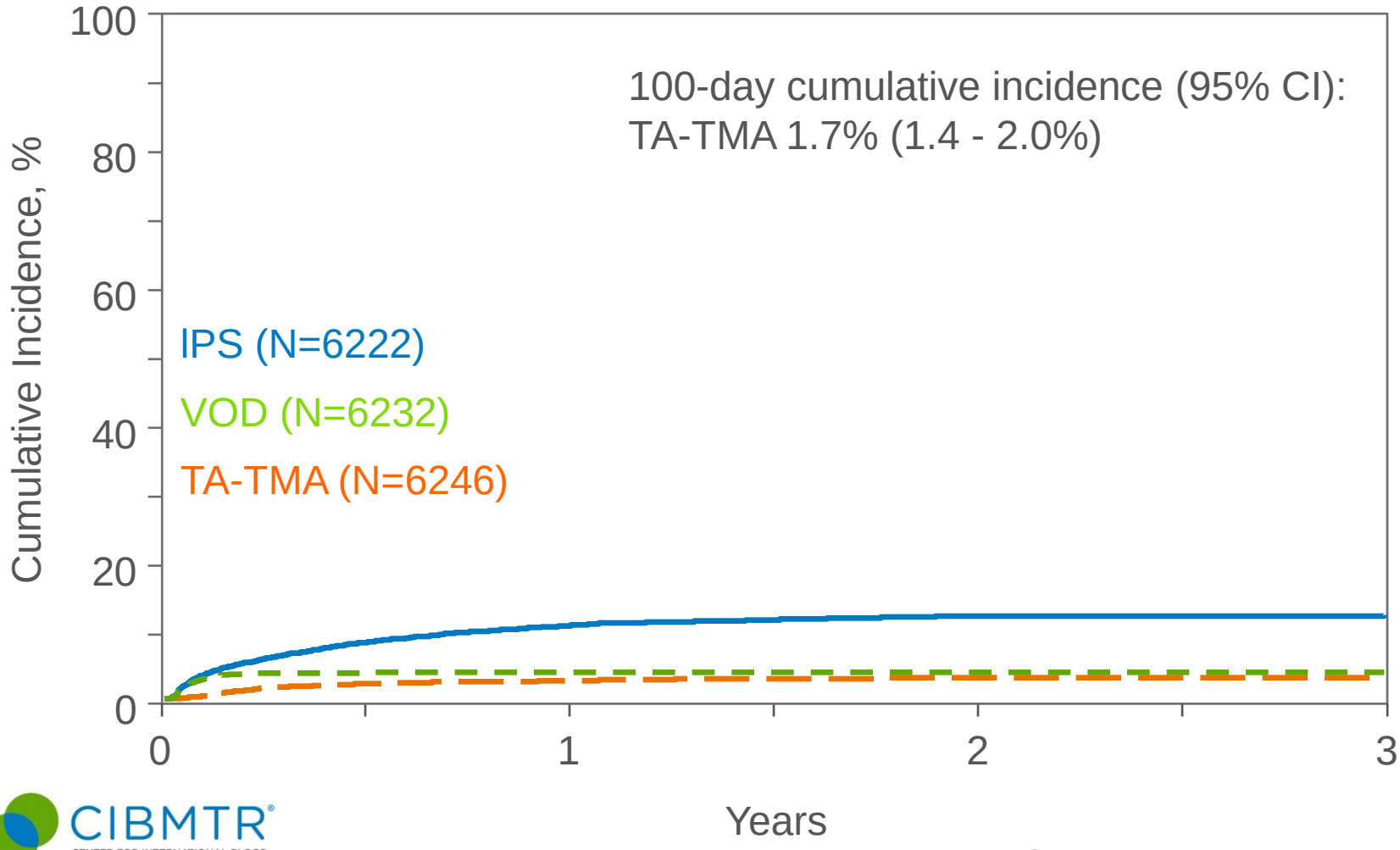
*Laskin BL, et al. Blood 2011. 118: 1452-1462
*Ruutu T, et al. BJH 2002. 118: 1112-1119

Cumulative Incidence of Post-HCT TMA



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Year of HCT: 2008-2012

Table 1. Current diagnostic guidelines for TA-TMA

Category	Blood and Marrow Transplant Clinical Trials Network[18]	International Working Group of the European Group for Blood and Marrow Transplantation[58]	Probable TMA as defined by validation study by Cho et al[53]
Schistocytes	$\geq$ 2 per high-power field in peripheral blood	$>$ 4% in peripheral blood	$\geq$ 2 per high-power field in peripheral blood
LDH	Increased above institutional baseline	Sudden and persistent increase	Increased
Renal function	Doubling of serum creatinine or 50% decrease in creatinine clearance from baseline before transplantation		
Platelets		Thrombocytopenia: $< 50 \times 10^9$/L or a $\geq$ 50% decrease in platelet count	Thrombocytopenia: $< 50 \times 10^9$/L or a $\geq$ 50% decrease in platelet count
Red cells		Decreased hemoglobin or increased red blood cell transfusions	Decreased hemoglobin
CNS	Unexplained neurologic dysfunction		
Coombs test	Negative direct and indirect		Negative
Haptoglobin		Decreased	Decreased
Other			No coagulopathy

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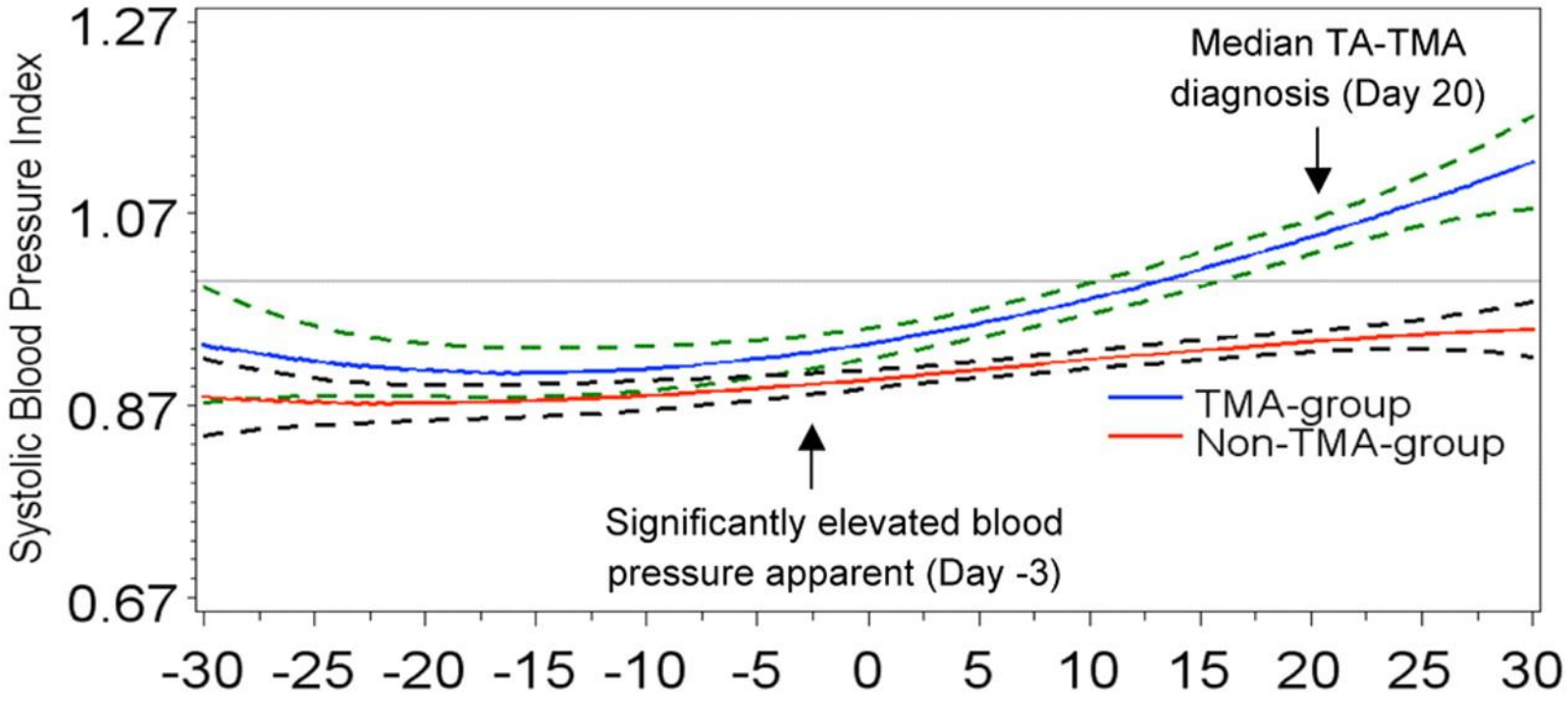
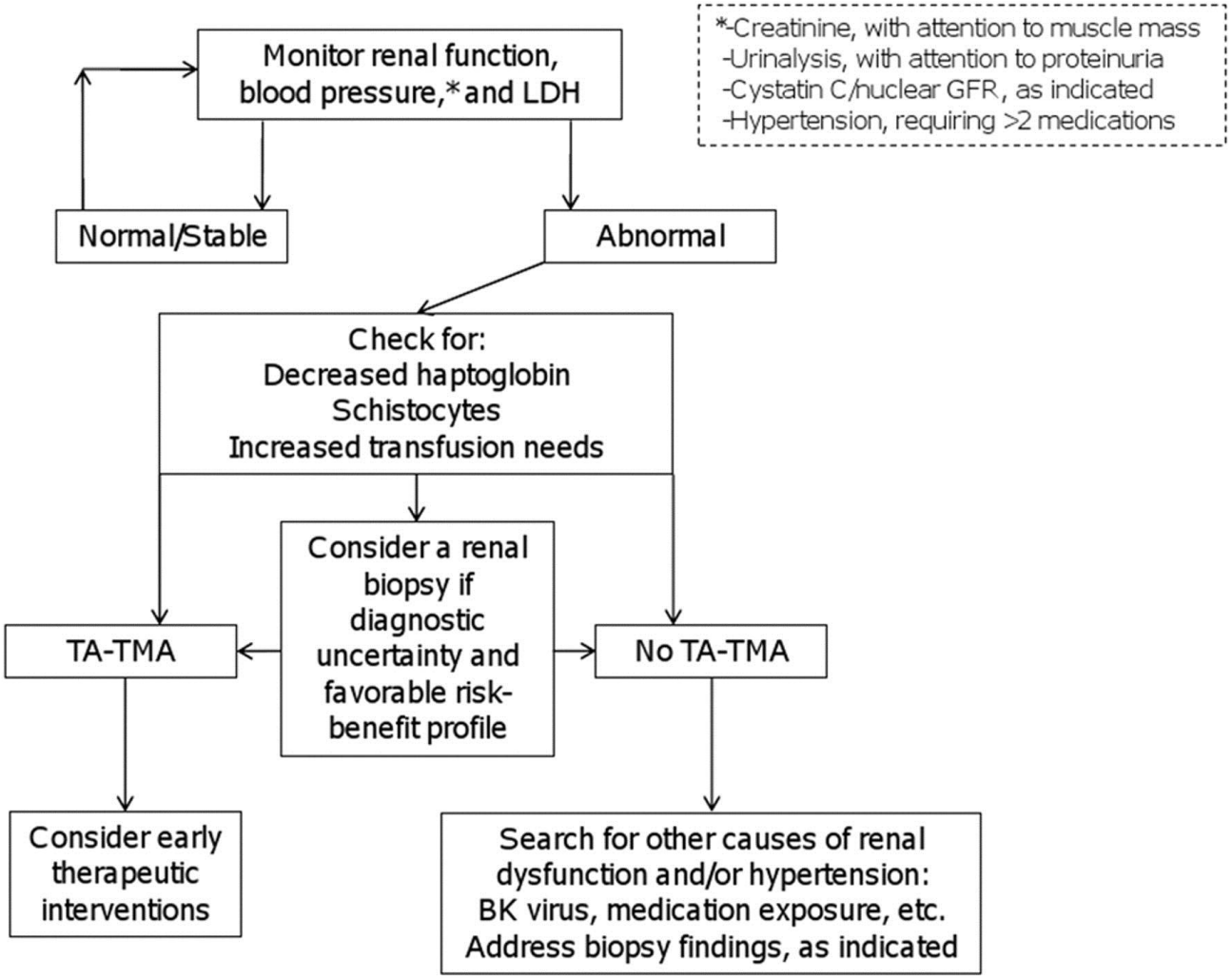
Elevated systolic blood pressure 3 days before stem cell infusion predicted later TA-TMA.



Laskin B L et al. Blood 2011;118:1452-1462

A “renal-centric” approach to detect TA-TMA.



Laskin B L et al. Blood 2011;118:1452-1462

Proposed Risk Factors

- Transplant type: Allogeneic HCT vs. autologous HCT
- Busulfan, fludarabine, platinum based chemotherapy
- TBI
- Fungal and viral infections
- Calcineurin inhibitors
- Use of sirolimus
- GVHD
- Coagulation cascade and role of complement

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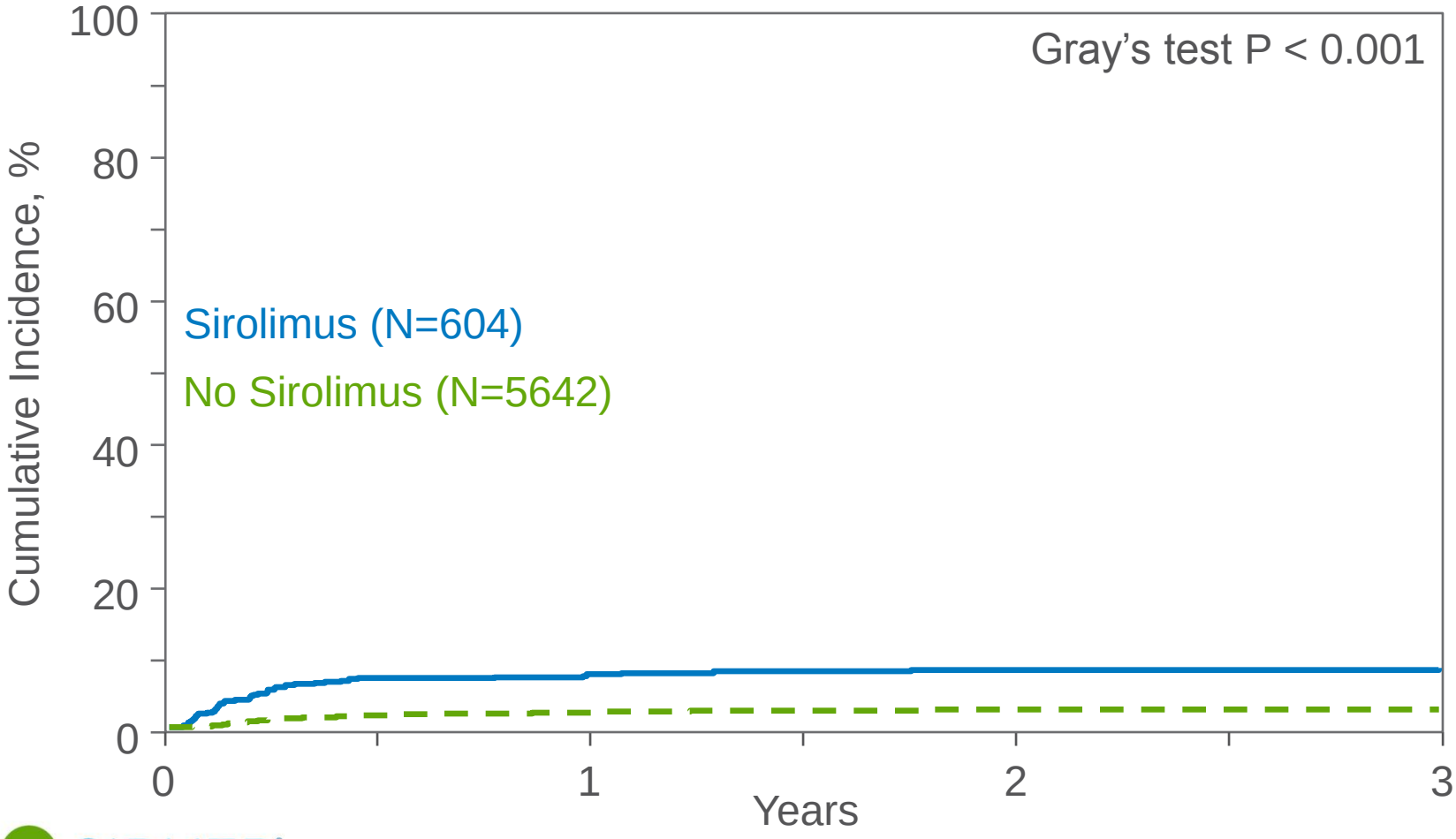
*Laskin BL, et al. Blood 2011. 118: 1452-1462

By Sirolimus Use



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Year of HCT: 2008-2012

Non-significant Factors

- Age
- KPS
- Graft source
- Conditioning regimen intensity
- TBI
- Busulfan

Serum Neutrophil Extracellular Trap level as a novel biomarker of TA-TMA

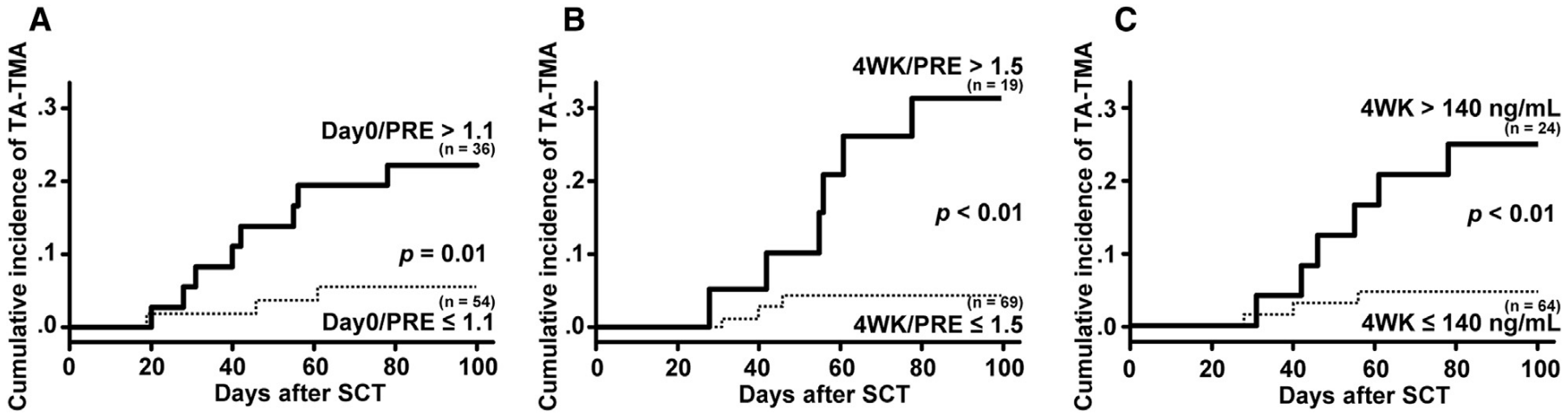

Figure 3. High NET levels are a risk factor for TA-TMA. (A) The incidence of TA-TMA relative to the Day0/PRE serum NET ratios. (B) The incidence of TA-TMA relative to the 4WK/PRE serum NET ratios. (C) The incidence of TA-TMA relative to absolute serum NET levels at 4WK. Note that elevations of either the serum NET ratios (Day0/PRE and 4WK/PRE) or absolute NET levels at 4WK are significant risk factors for TA-TMA.

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Arai Y, et al. BBMT 19 (2013) 1683-1689

NET levels and risk of TA-TMA

- In multivariate analysis:

- Day 0 NET/Pre, over/under 1.1:

RR 3.55 (1.03-12.2; p=.04)

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Arai Y, et al. BBMT 19 (2013) 1683-1689

Therapy

- PE
- Withdrawal of CI
- Rituximab
- Novel agents

➔$$$

Early Recognition

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*Laskin BL, et al. Blood 2011. 118: 1452-1462

IPS

- Acute noninfectious lung injury
- Incidence 2% -10%
- a median time of onset 14-42 days post HCT
- CIBMTR: 100-day incidence of 6.2% (95% CI 5.7-6.9)
- Associated with high mortality rates (>50%)

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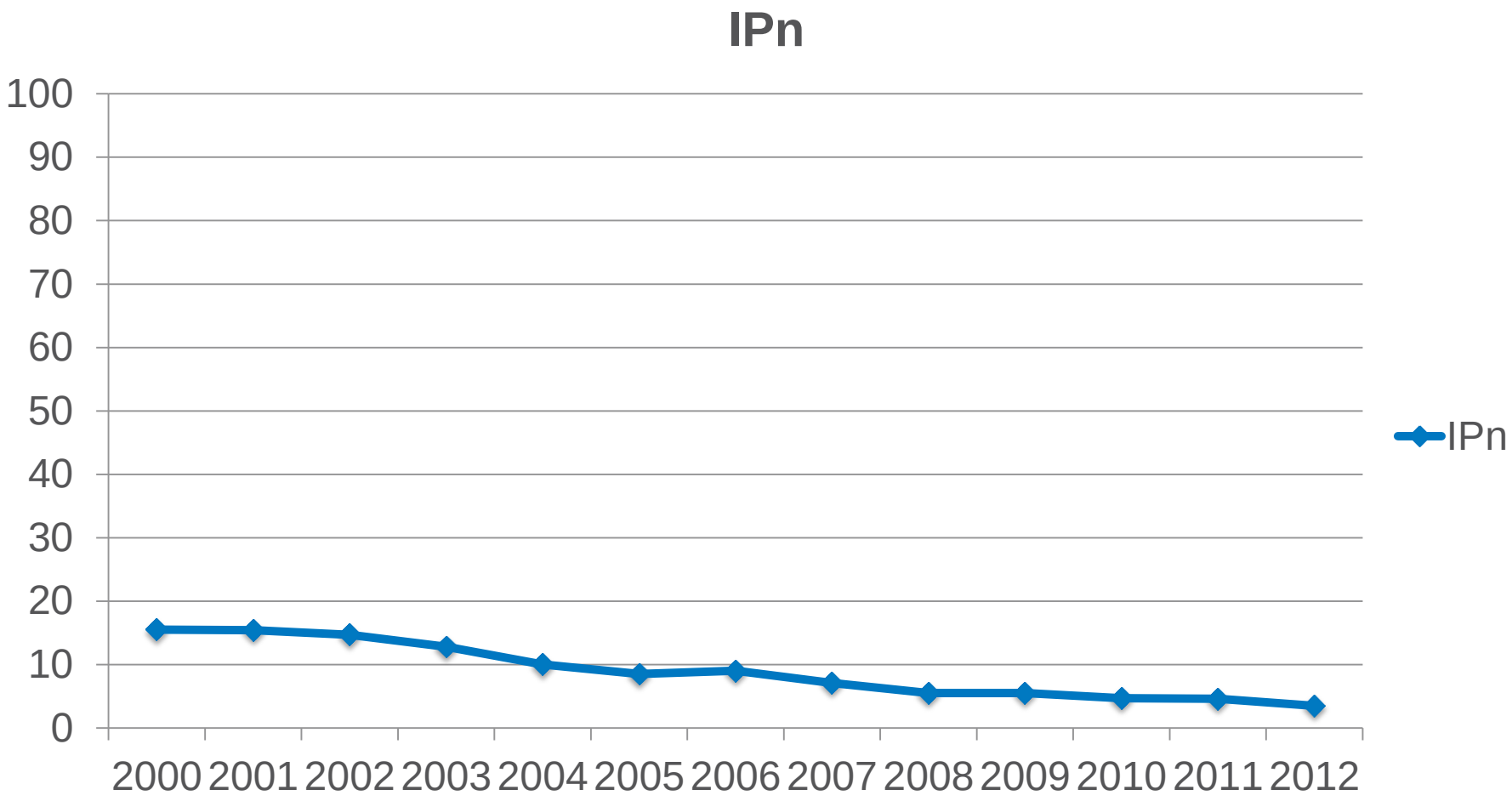
*Yanik GA, et al. BBMT 2014. 858-864

Development of Organ Disease in First 100 Days Post-HCT



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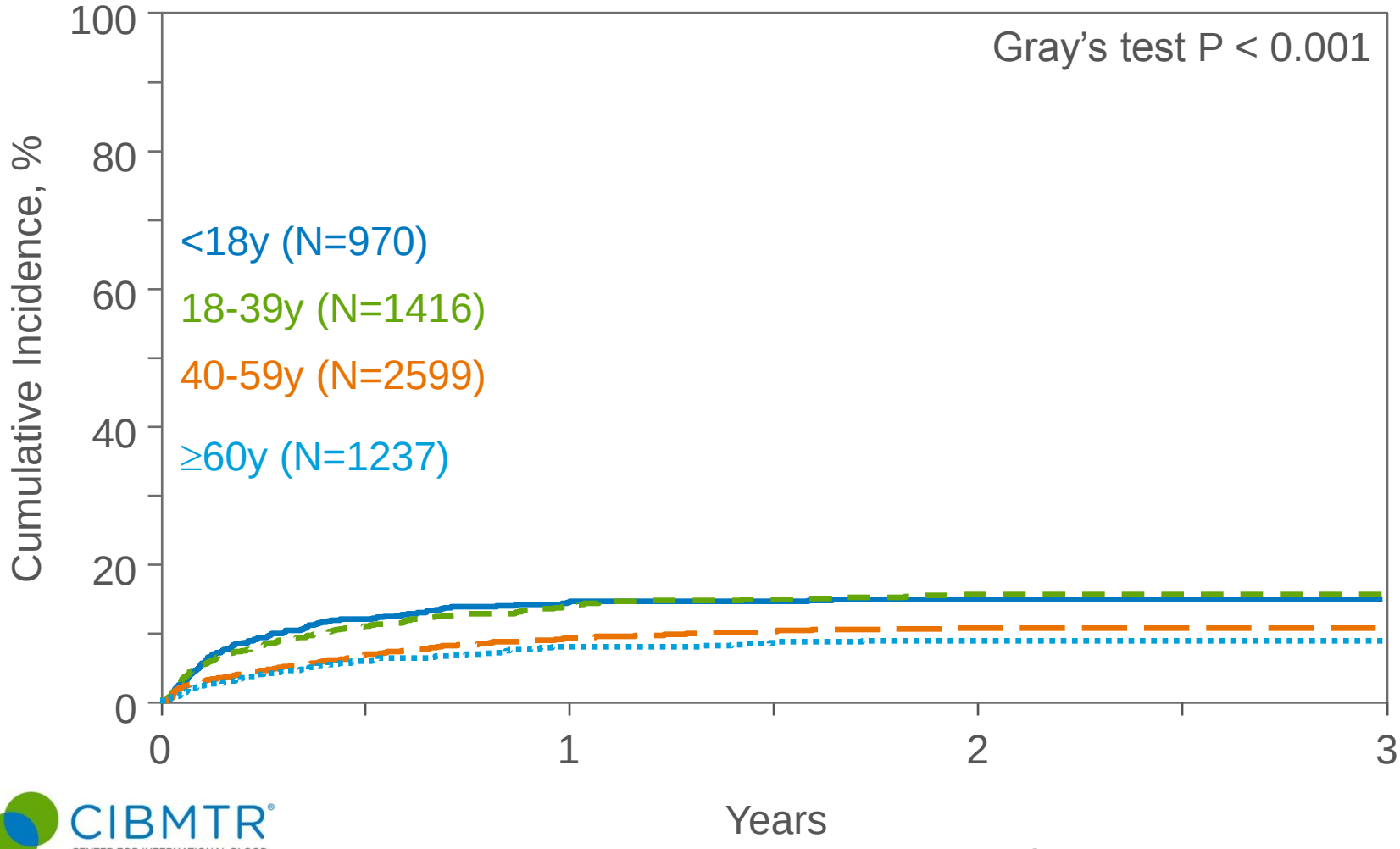
Incidence by Age at HCT



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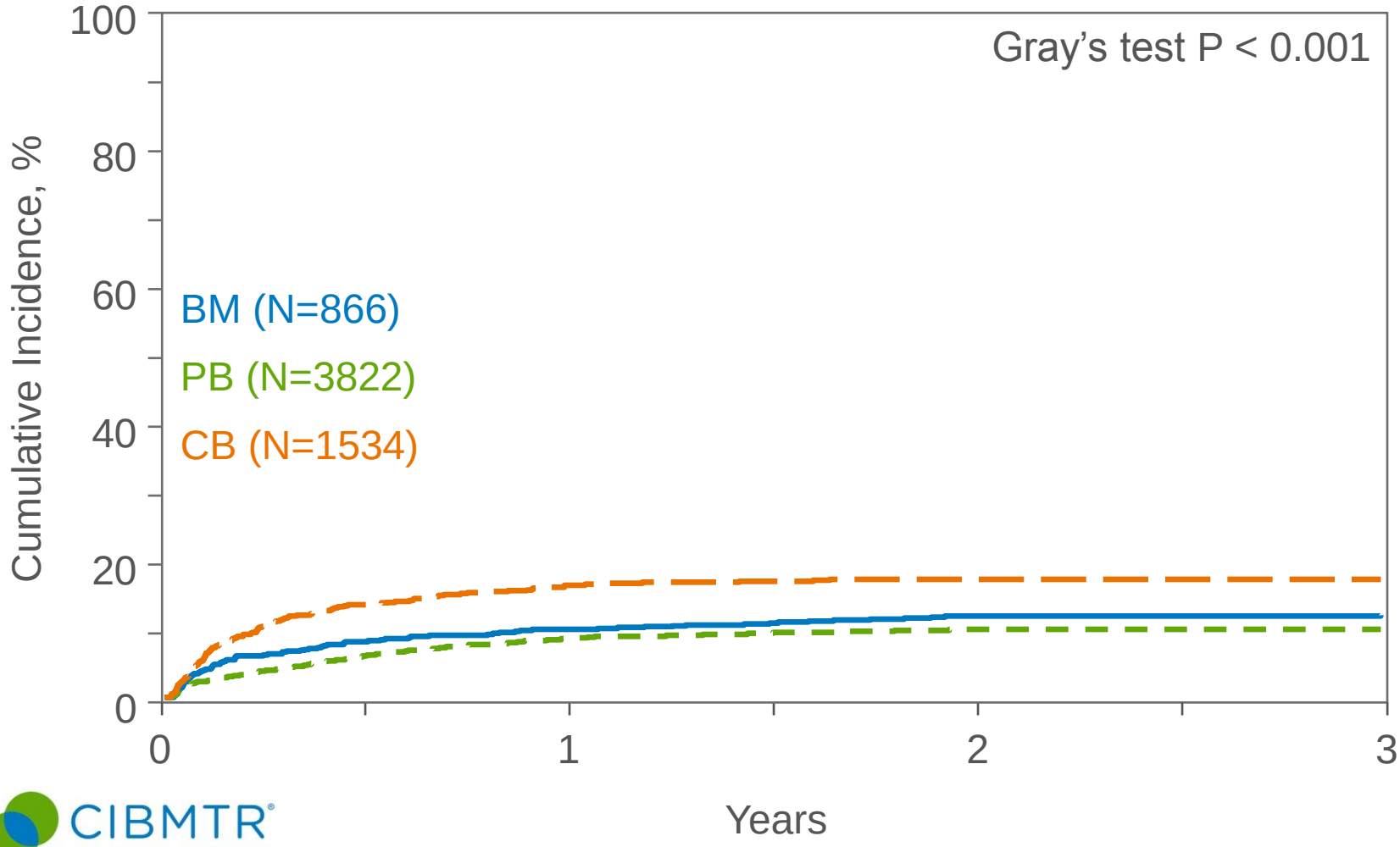
Year of HCT: 2008-2012

By Graft Source



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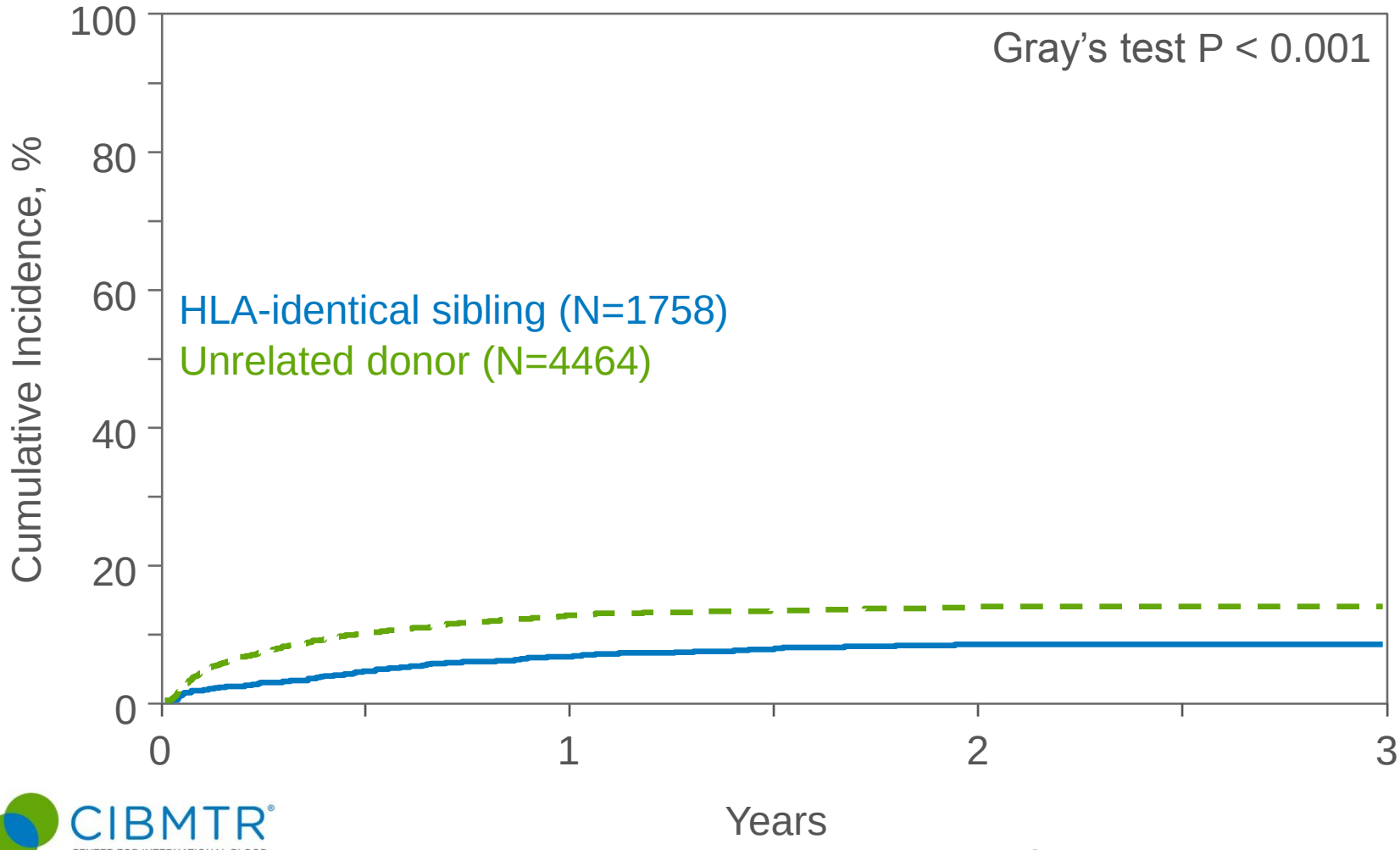
Year of HCT: 2008-2012

By Donor Type



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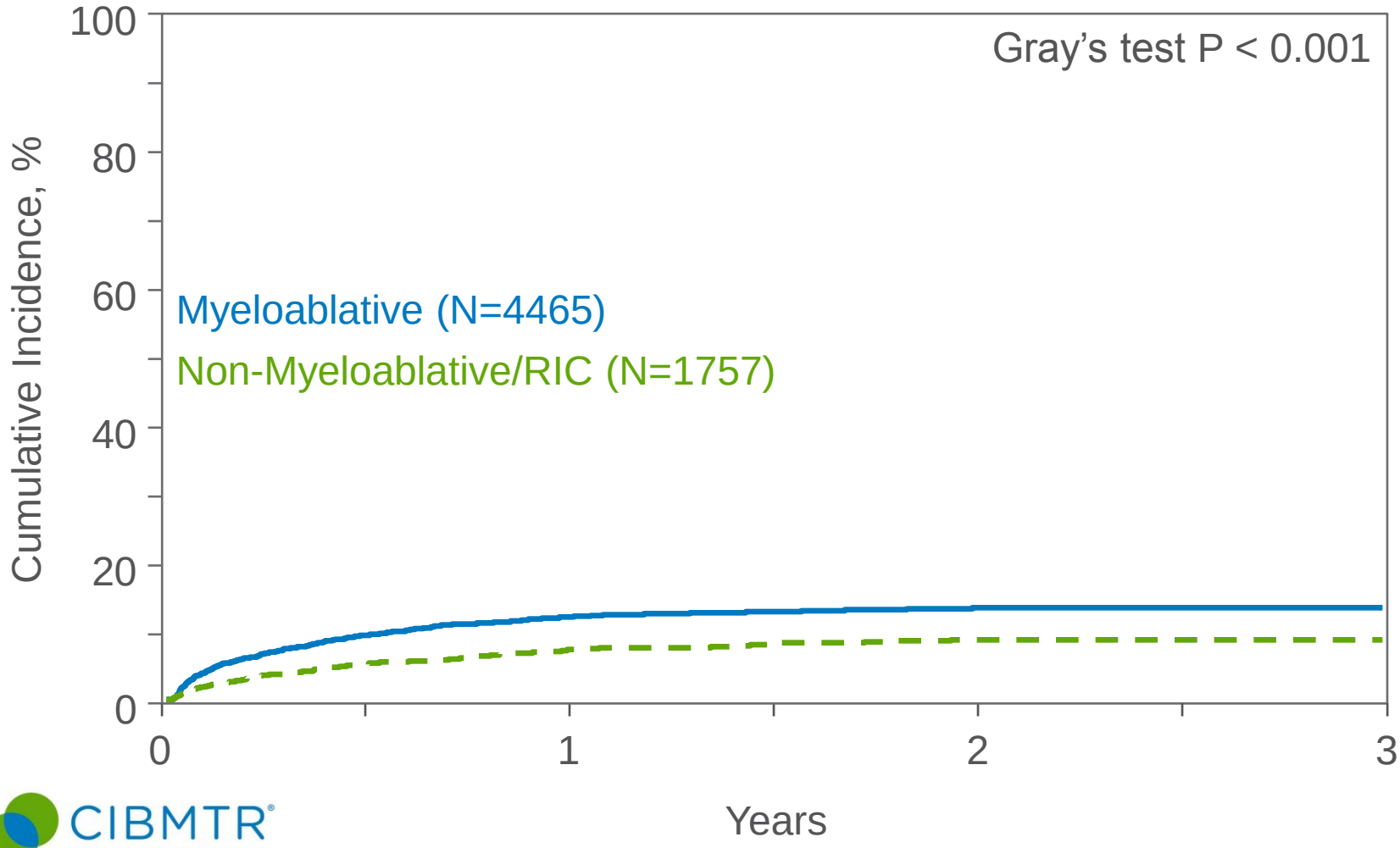
Year of HCT: 2008-2012

By Conditioning Regimen Intensity



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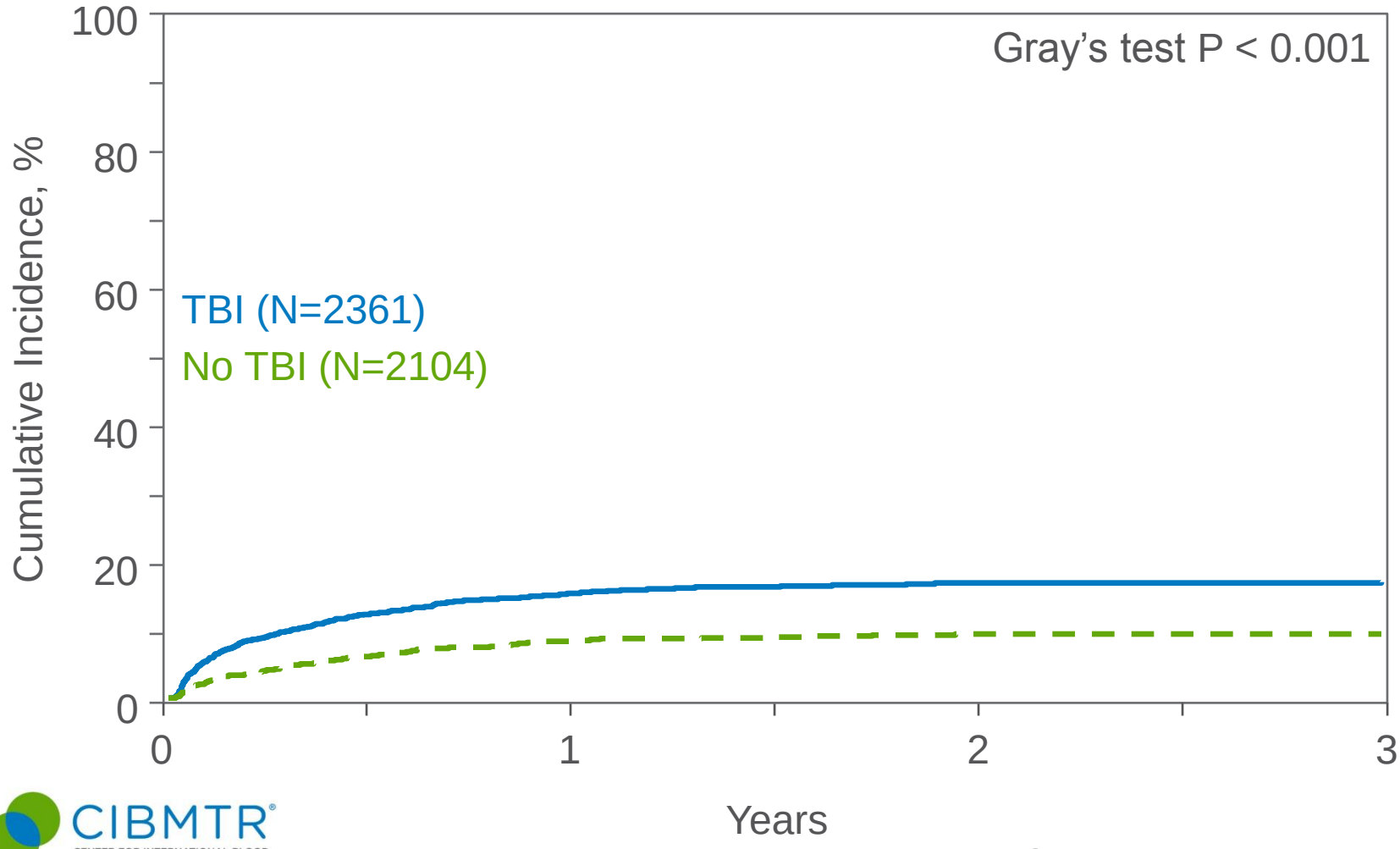
Year of HCT: 2008-2012

By TBI Use - Myeloablative Conditioning Regimens Only



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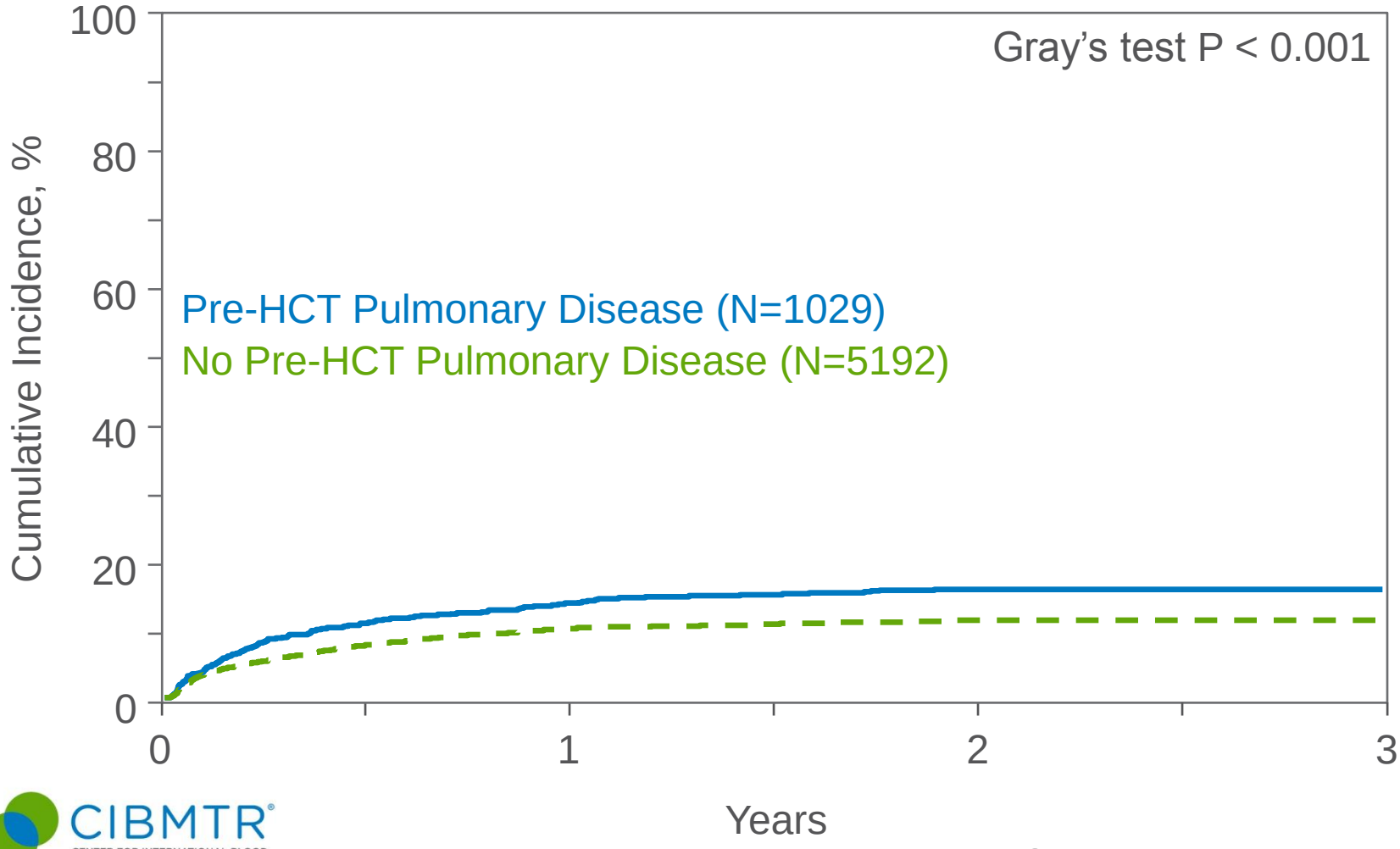
Year of HCT: 2008-2012

By Presence of Pulmonary Disease Pre-HCT



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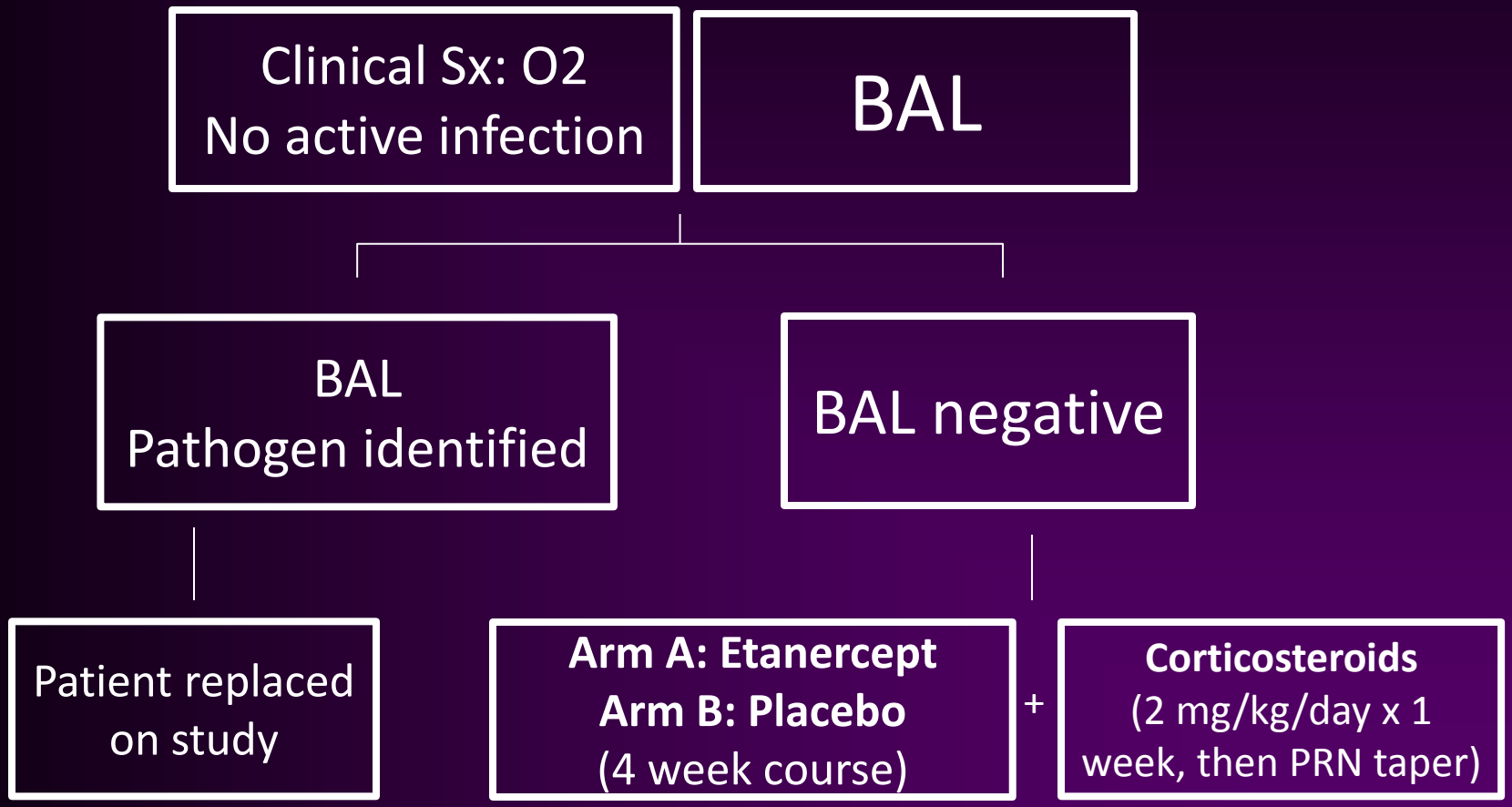
Year of HCT: 2008-2012

Study schema: BMT CTN 0403



*Yanik GA, et al. BBMT 20 (2014) 858-864

Response Rates: BMT CTN 0403

Therapy	Etanercept + steroids (n=16)	Placebo + steroids (n=18)
Day 28 Response (%)	62.5% (95% CI: 35.4-84.8)	66.7% (95%CI: 41.0-86.7)
Day 56 Response (%)	56.3% (95% CI: 29.9–80.3)	50.0% (95% CI: 26.0-74.0)

p = 0.80

*Yanik GA, et al. BBMT 20 (2014) 858-864

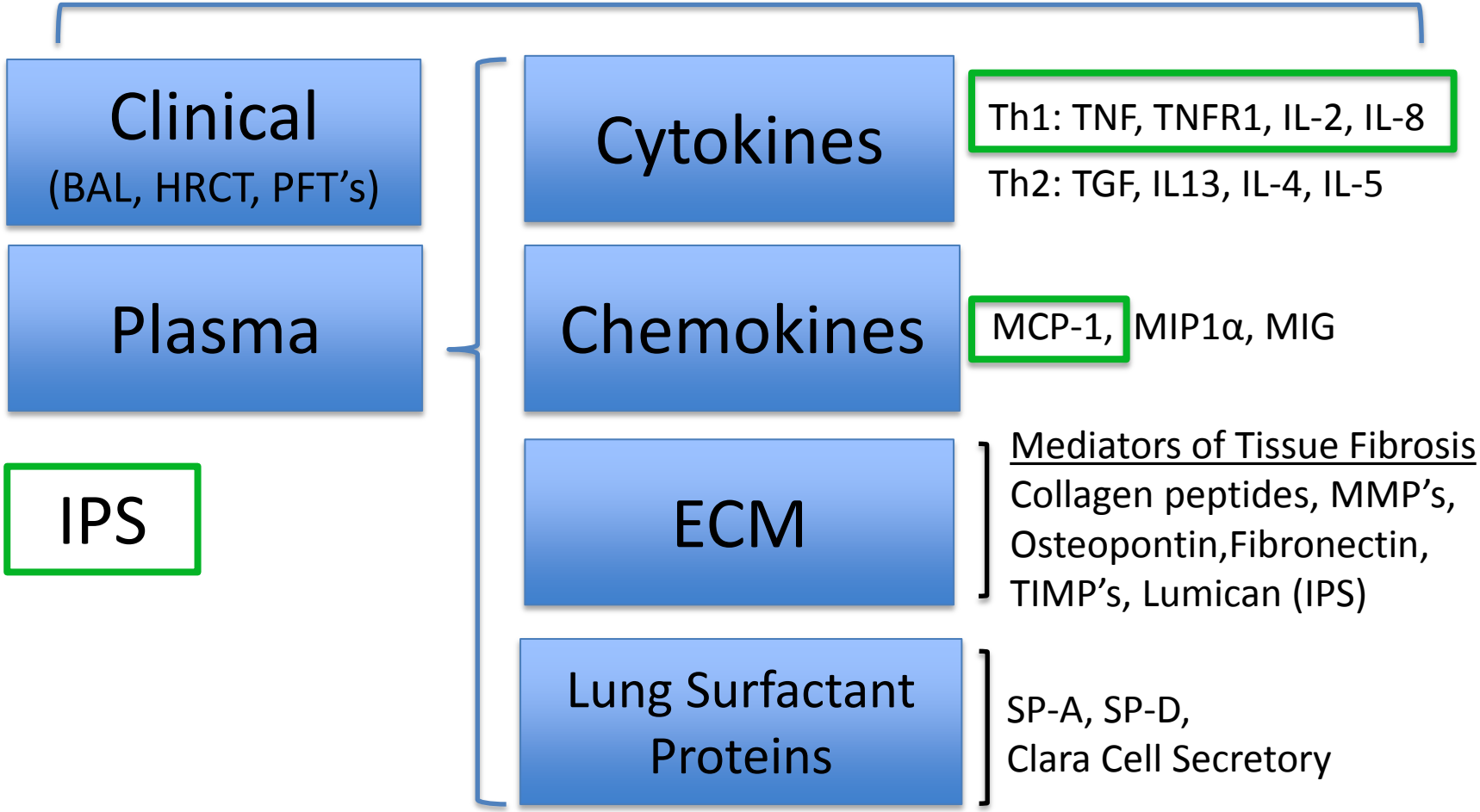
Response and FiO2 at study entry

BMT CTN 0403:

- Responses were higher if treated at lower FiO2.
- Median FIO2 at study entry = 40%

Response by % FiO2 at study entry			
	≤ 40%	> 40%	Unknown
Etanercept + steroids	8/11 (73)	2/4 (50)	0/1
Placebo + steroids	10/11 (91)	1/6 (17)	1/1

Biomarkers in Lung injury



BMT CTN 1202 Protocol

Biomarker Approach	Sample Type	Subjects	Pre-HCT day -1 or 0	Days Post-HCT						
				7	14	21	28	42	56	90
				±2	±2	±2	±2	±3	±3	±10
Proteomic	Serum (5 mL blood)	1500 patients	X	X	X	X	X	X	X	X
	EDTA plasma (5 ml blood)		X	X	X	X	X	X	X	X
Gene Expression	PAXgene Lysates-source WBC RNA (15 mL blood)	240 patients[1]				X			X	X
	CytoChex tube for Immunophenotyping (5 mL blood)	240 patients[1]				X			X	X

Conclusion

- VOD/TA-TMA/IPS are associated with poor survival post HCT
- Contemporary estimates of the cumulative incidences are lower than published data ➔ clinical trial design implications
- Emerging biomarkers should pave the way for better insight into pathogenesis and should guide future therapeutic trials

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Acknowledgments

- Mary Horowitz
- Paula Watry
- Corey Cutler
- Greg Yanik
- Terry Hahn
- Sandy Korman

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Value of a Consensus Panel to Adjudicate Cause-Specific Mortality after Unrelated Donor Allogeneic HCT for Use as the Primary Endpoint in a Genome-Wide Association Study (GWAS)

Theresa Hahn, PhD

Roswell Park Cancer Institute

Buffalo, NY

ROSWELL PARK CANCER INSTITUTE

Funding

- Supported by NHLBI R01
- HL 102278

- Genetic susceptibility to unrelated donor stem cell transplant-related mortality

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Objective

- Perform GWAS to test the contribution of recipient, donor, and R-D genetic variation to TRM by 1 year after URD HCT
- TRM is a complex phenotype, encompassing several subtypes (GVHD, infection, organ failure/RRT, other)
- Data and samples from CIBMTR/NMDP (>150 U.S centers)
- Risk of misclassification/confounding due to complex phenotype and reporting variability with high number of centers

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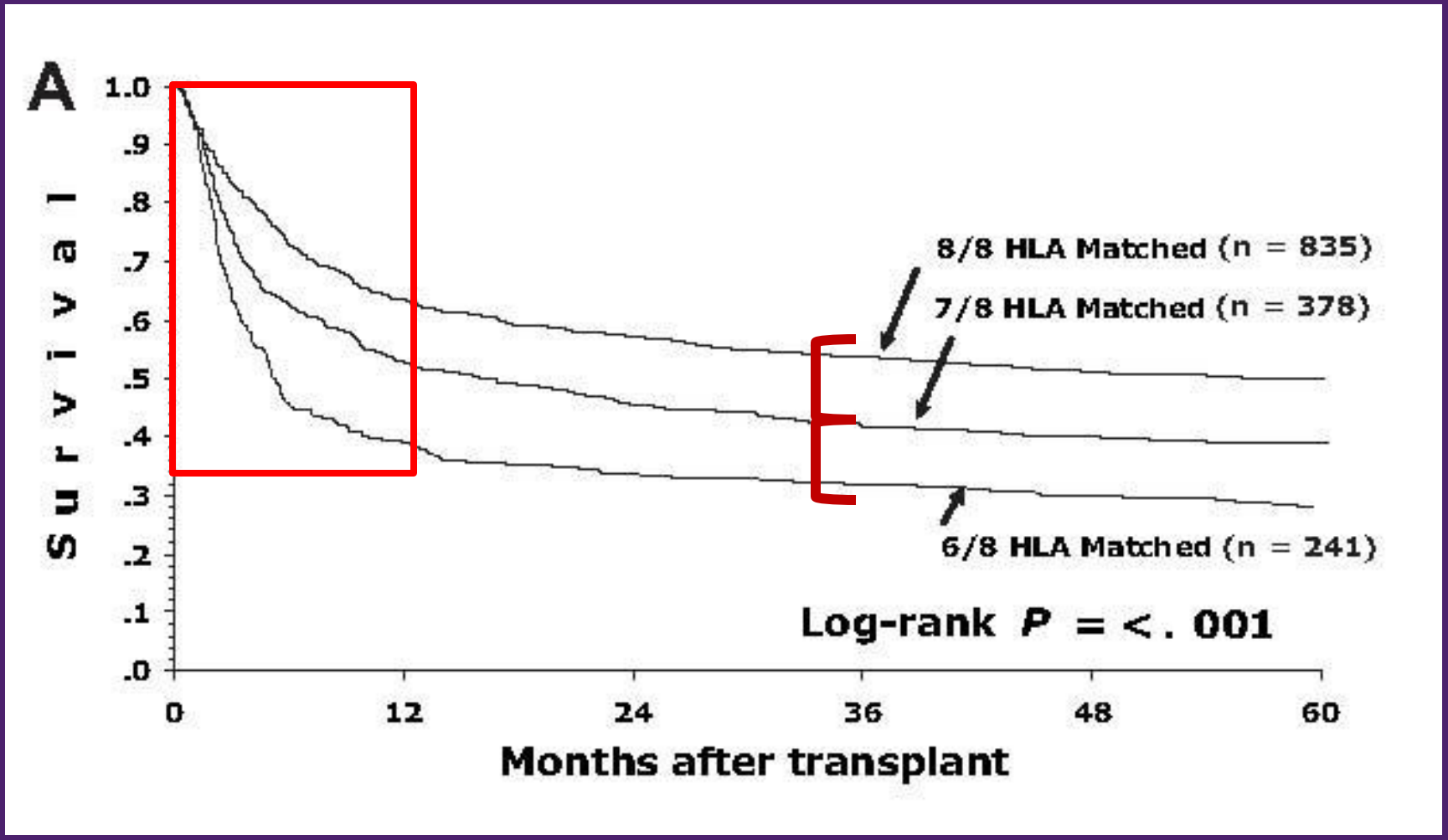
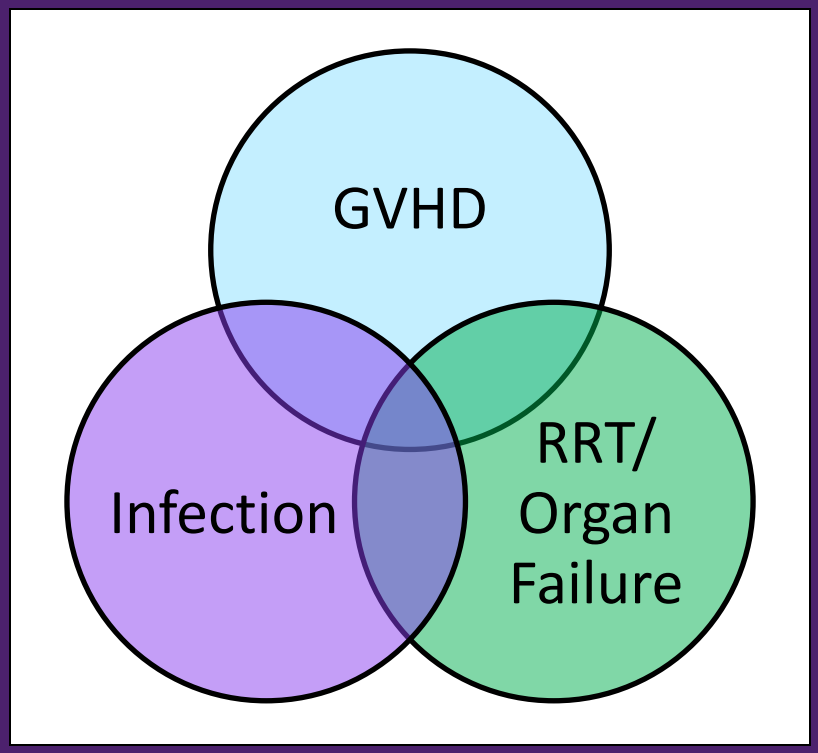
Majority of Deaths Occur <1 year post-HCT

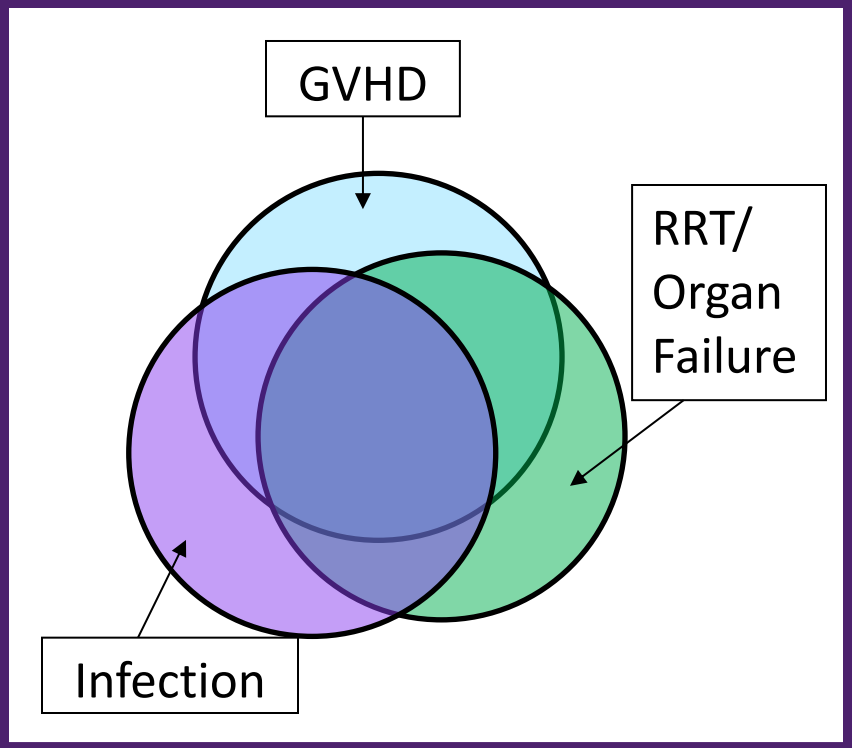


Lee, et al, Blood 2007

TRM subtypes may have unique and shared genetic variants



Genetic Variants Associated with TRM:
Unique Genetic Variants with **Little** overlap between TRM subtypes



Genetic Variants Associated with TRM:
Shared Genetic Variants with **Major** overlap between TRM subtypes

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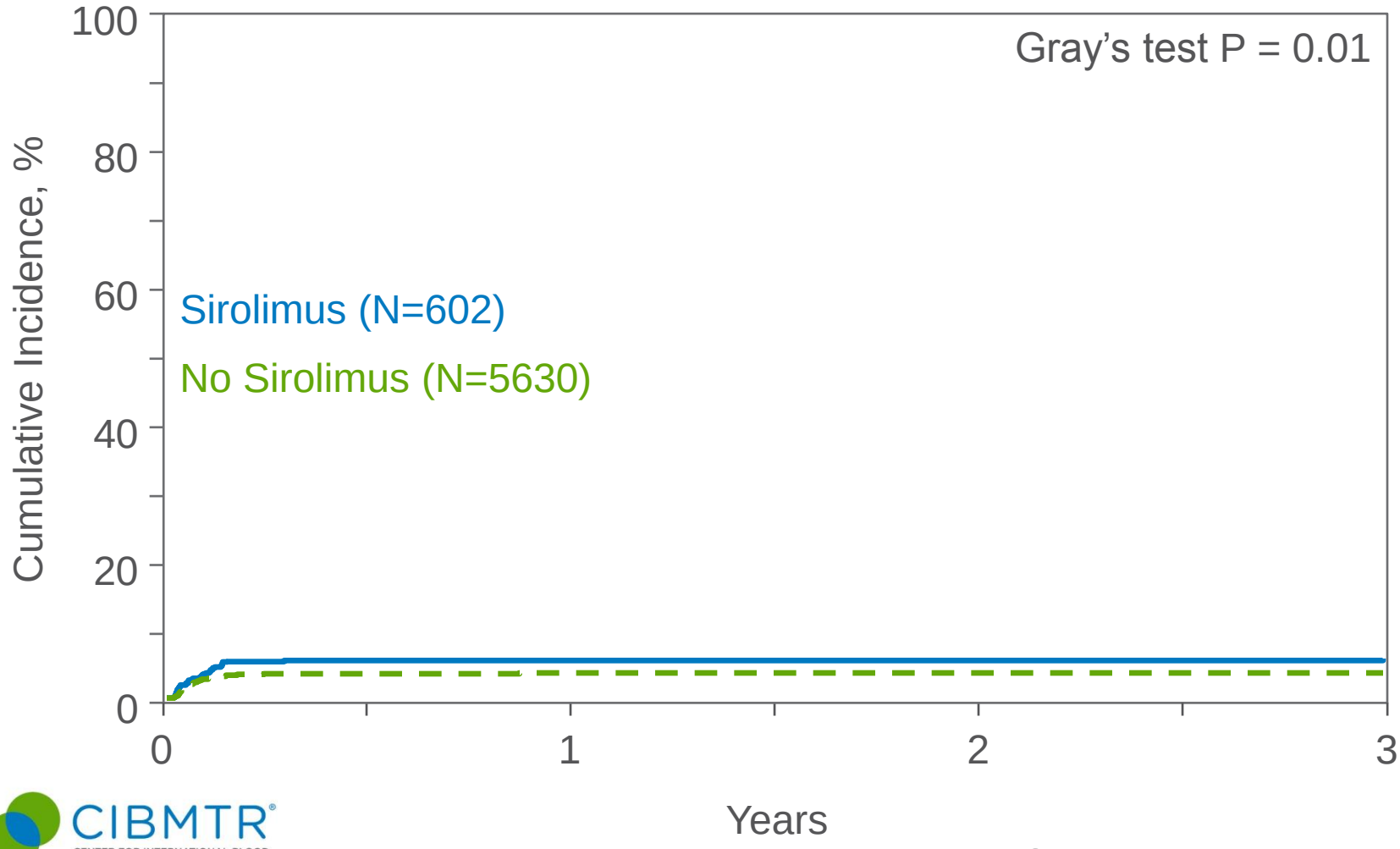
Incidence of Veno-Occlusive Disease by Sirolimus Use for GVHD Prophylaxis



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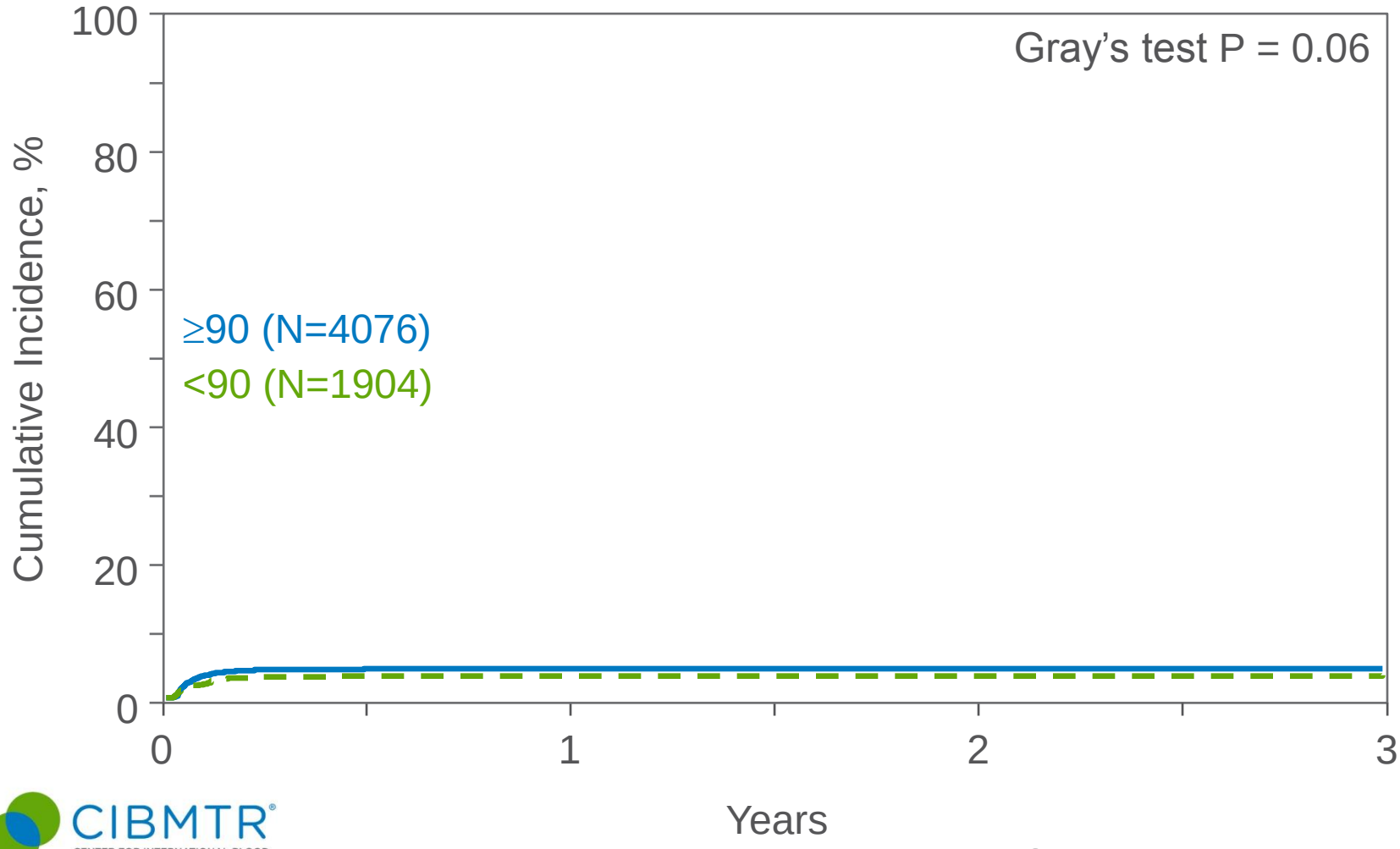
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by KPS



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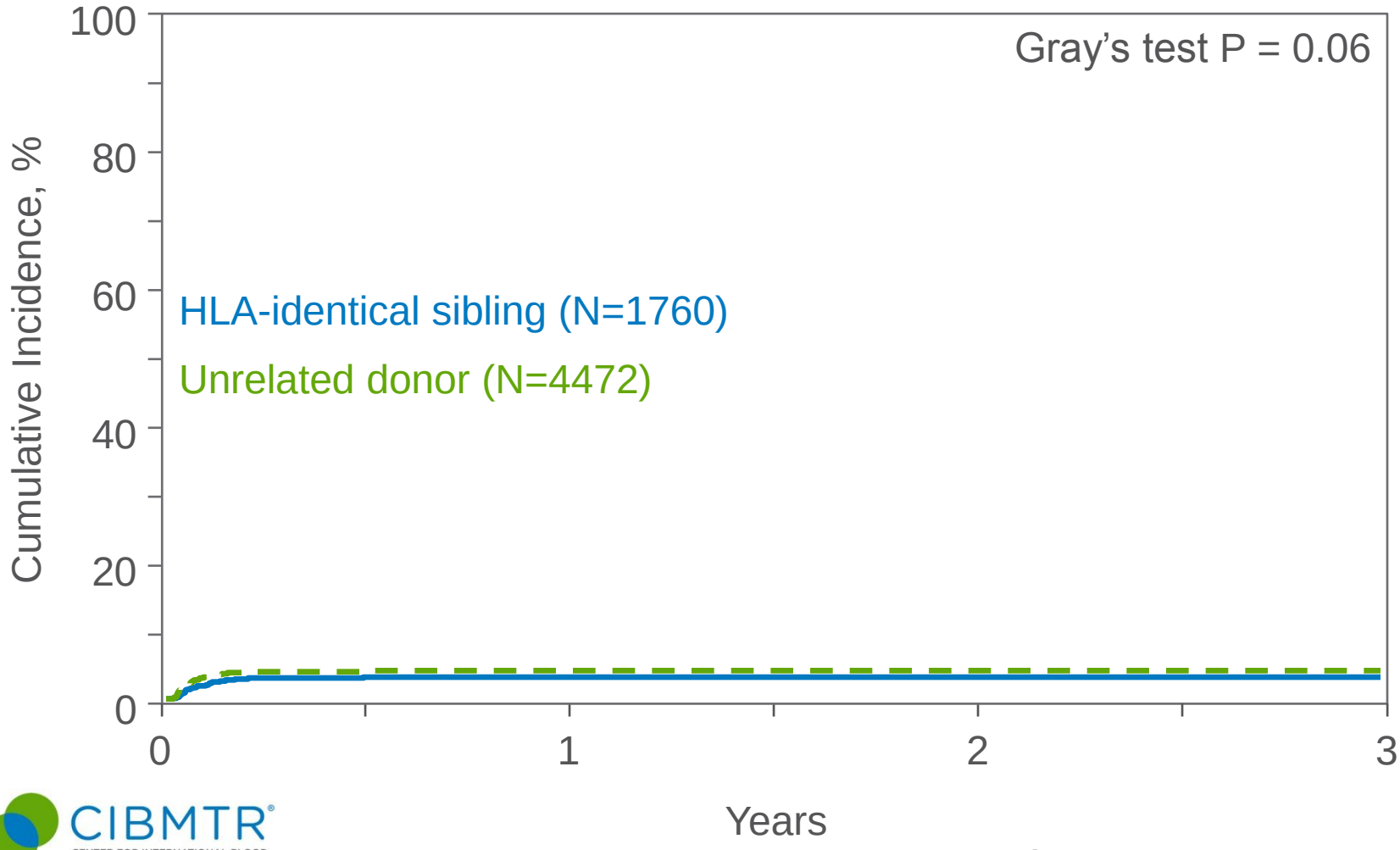
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by Donor Source



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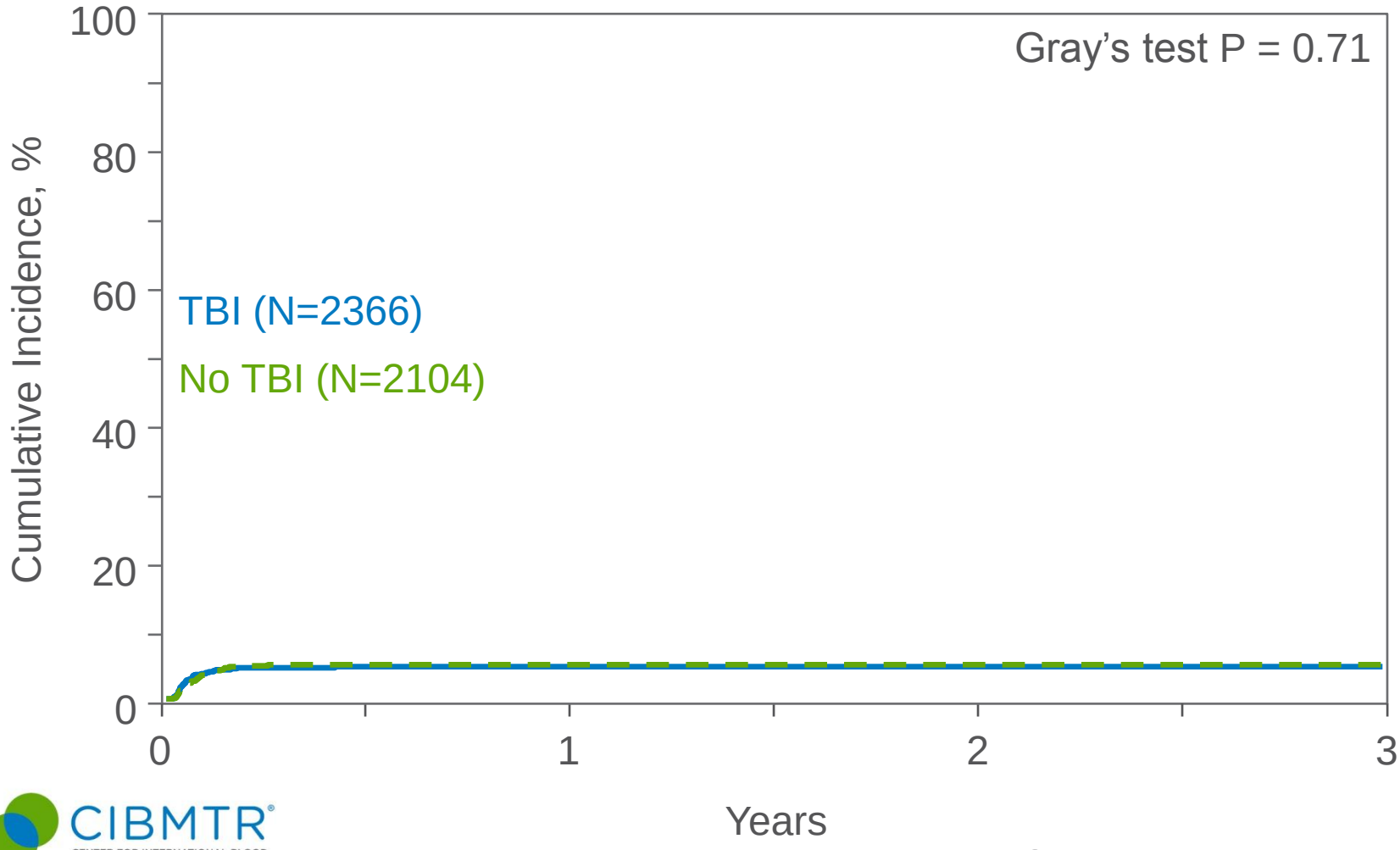
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by TBI Use - Myeloablative Conditioning Regimens Only



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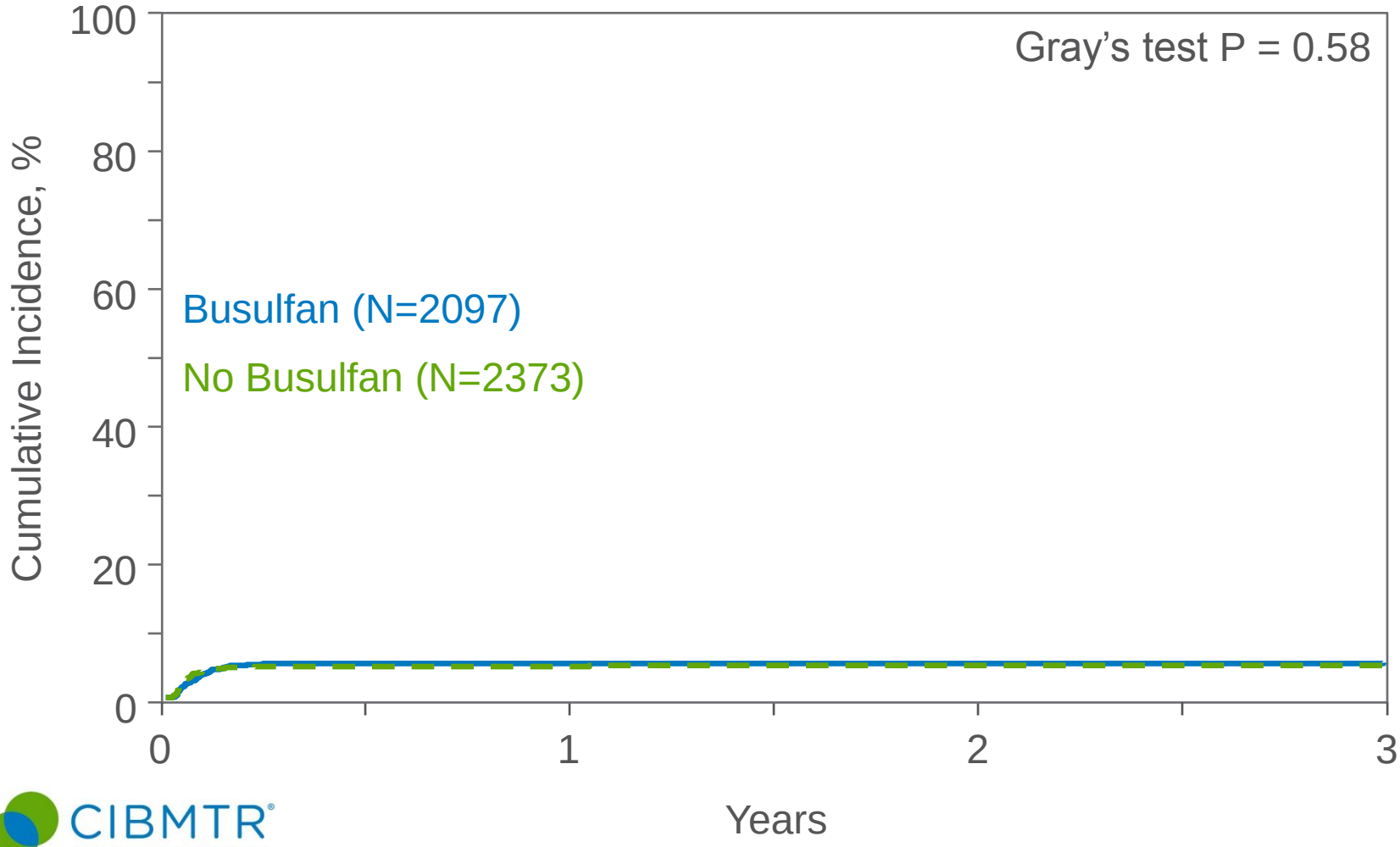
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by Busulfan Use - Myeloablative Conditioning Regimens Only



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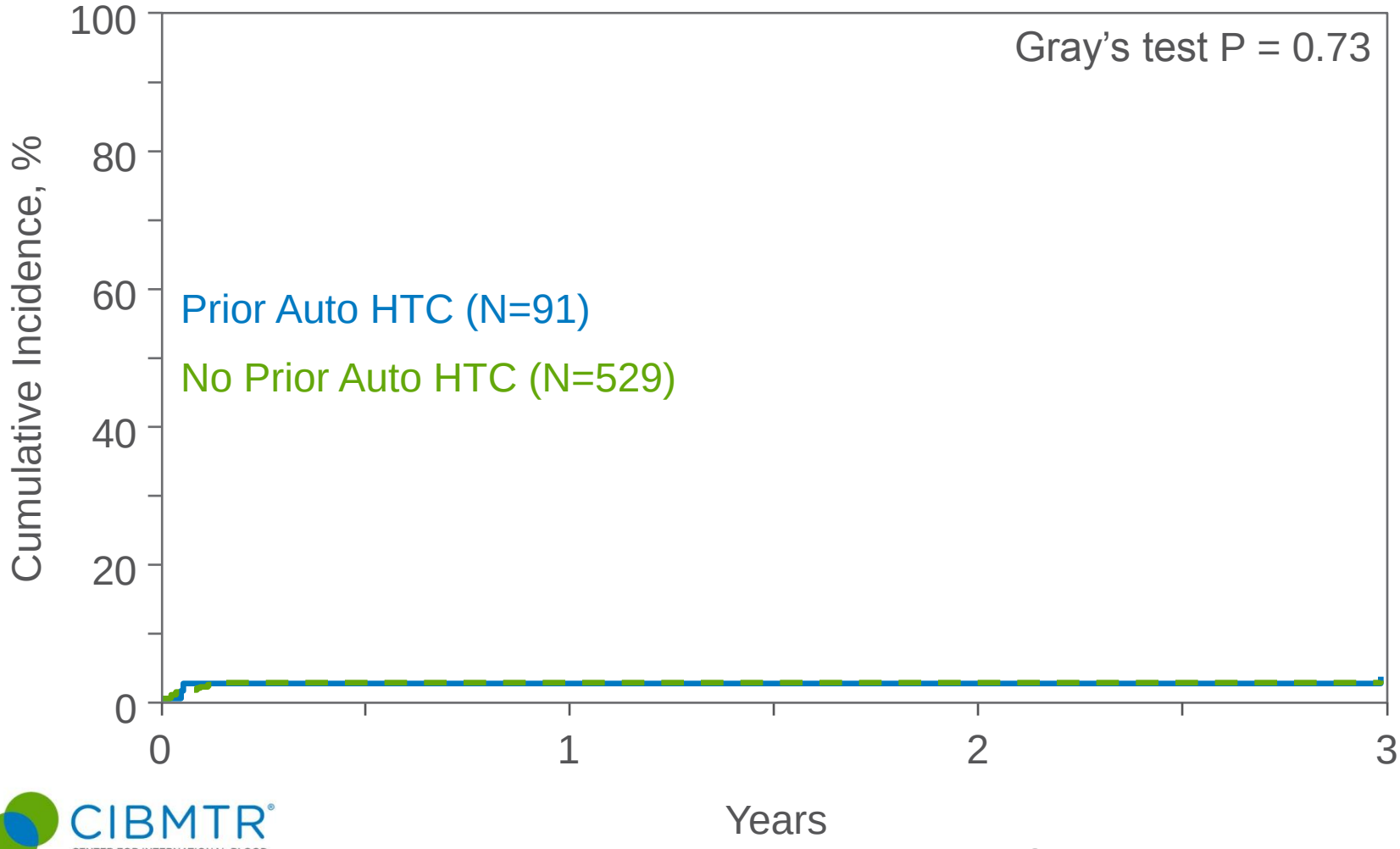
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by Prior Auto HCT - Patients with Non-Hodgkin Lymphoma Only



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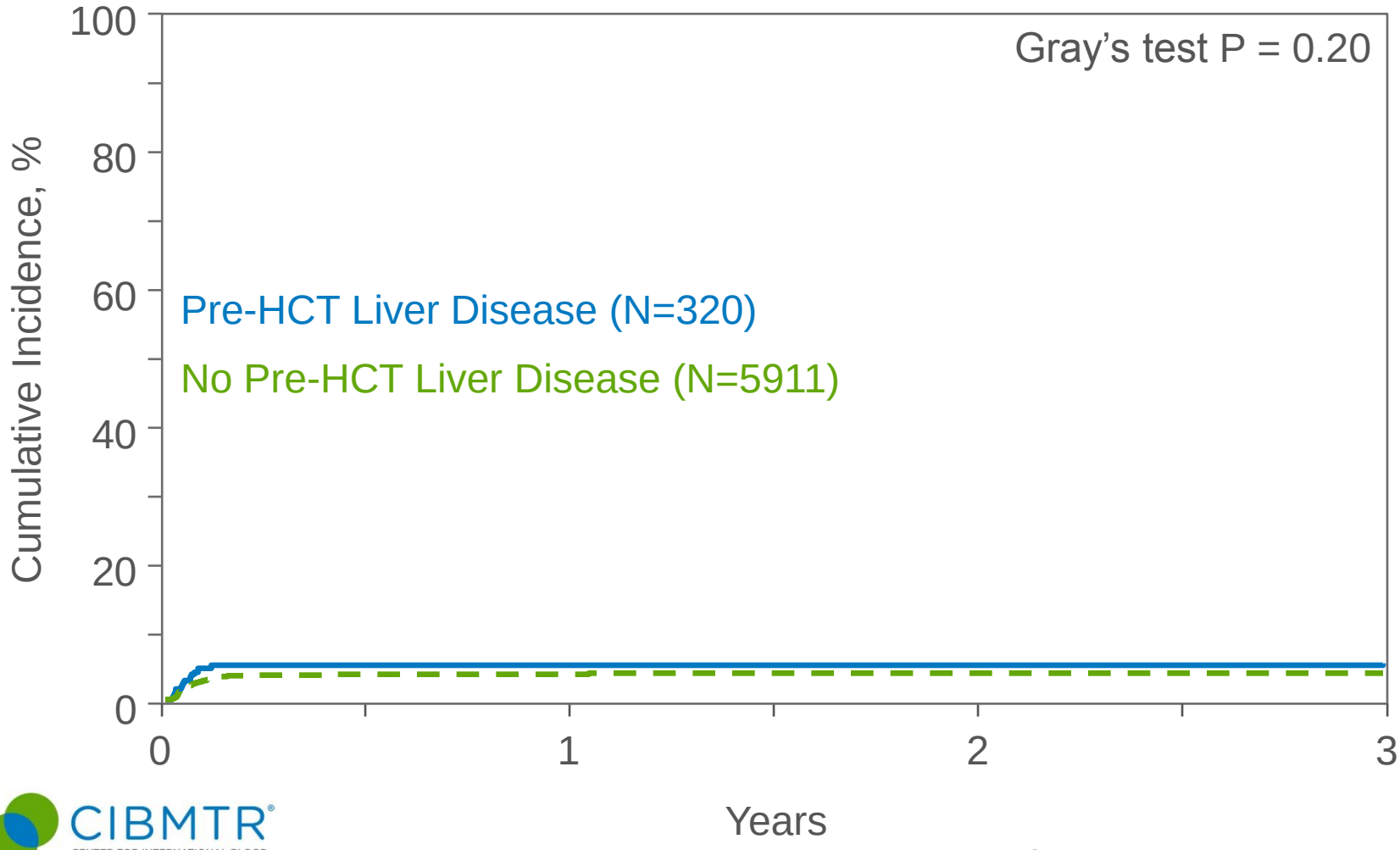
Incidence of Veno-Occlusive Disease by Presence of Liver Disease Pre-HCT



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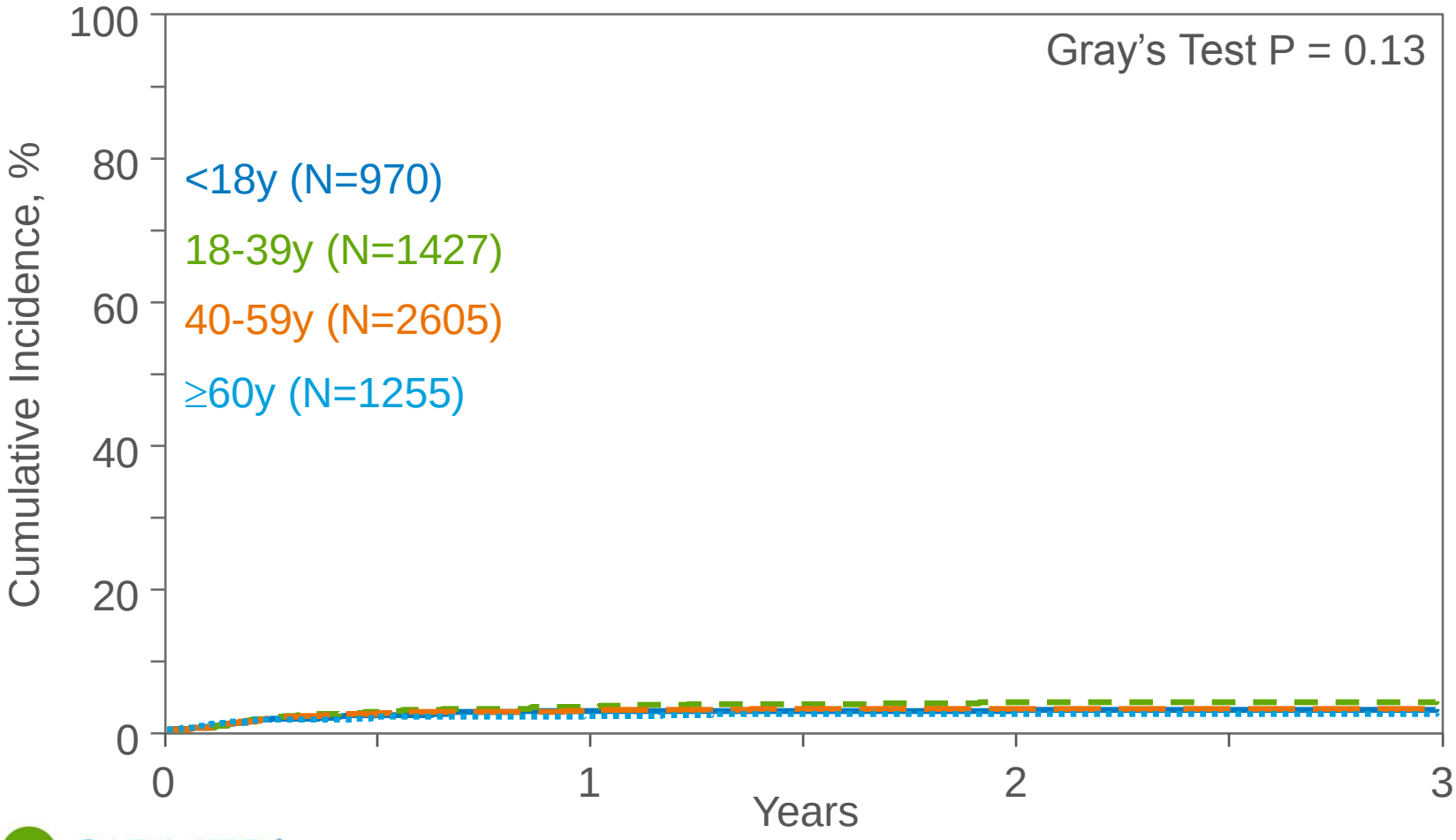
Year of HCT: 2008-2012

Incidence of TA-TMA by Age



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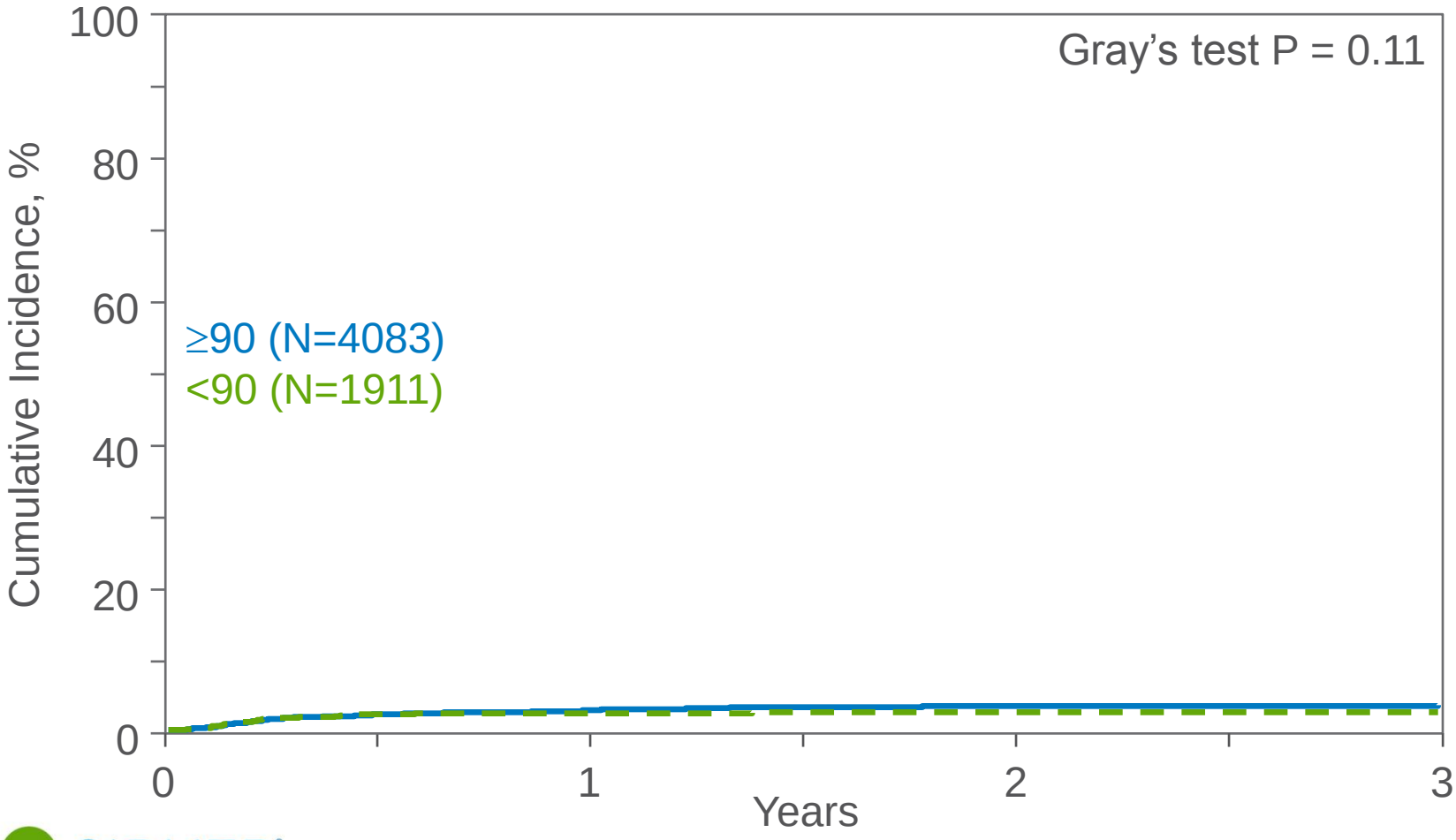
Year of HCT: 2008-2012

Incidence of TA-TMA by KPS



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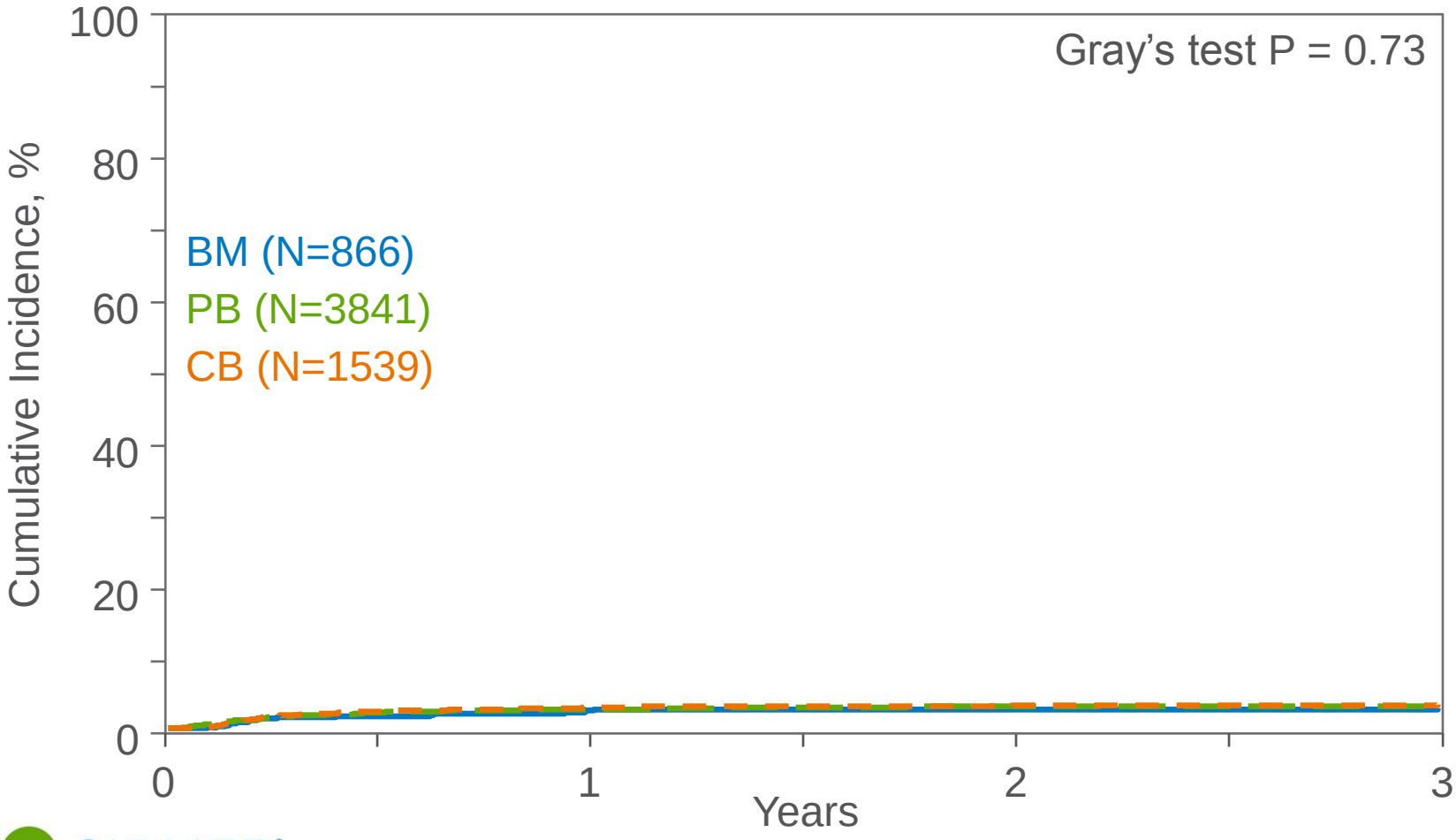
Incidence of TA-TMA by Graft Source



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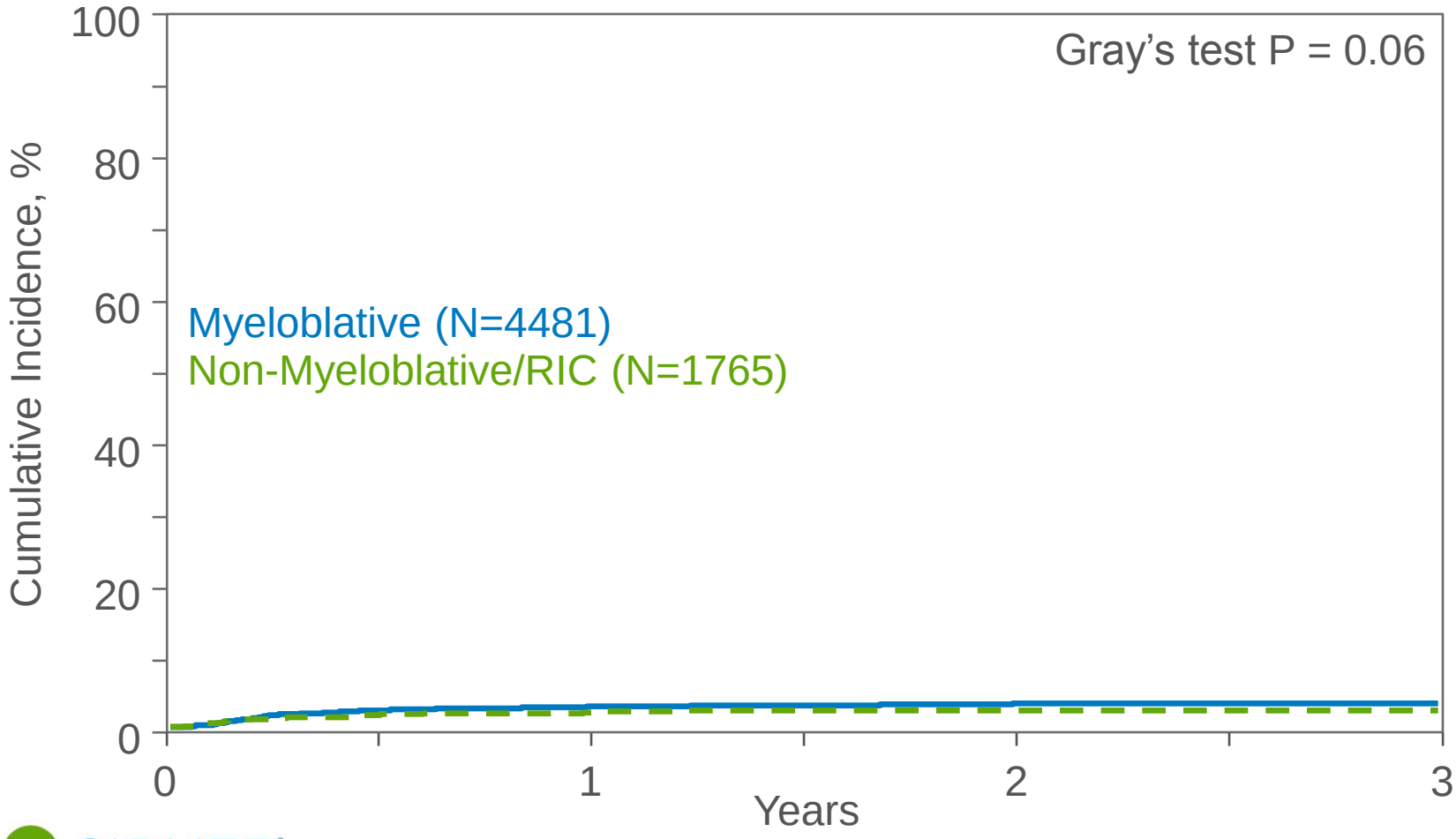
Incidence of TA-TMA by Conditioning Regimen Intensity



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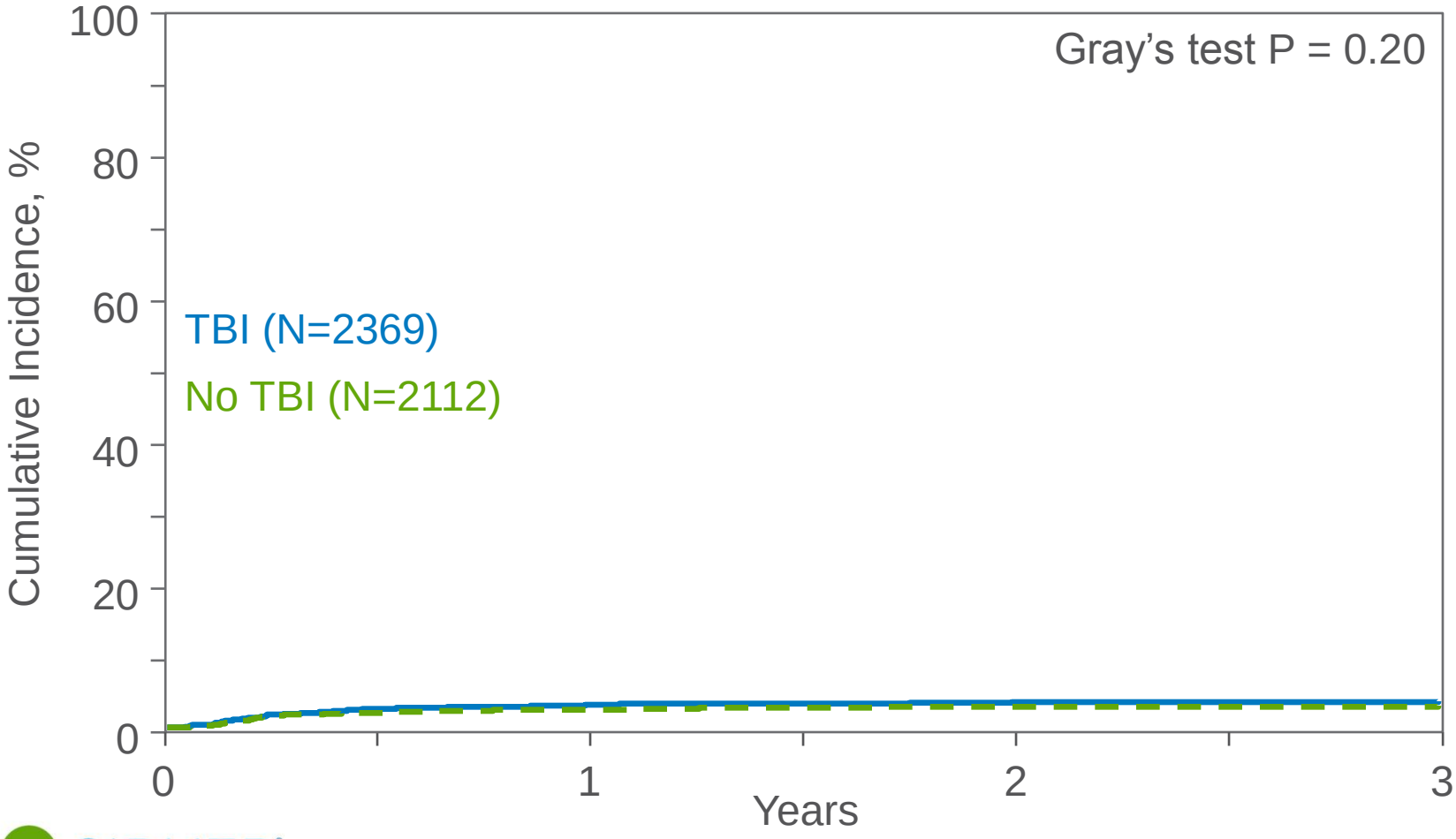
Incidence of TA-TMA by TBI Use Myeloablative Conditioning Regimens Only



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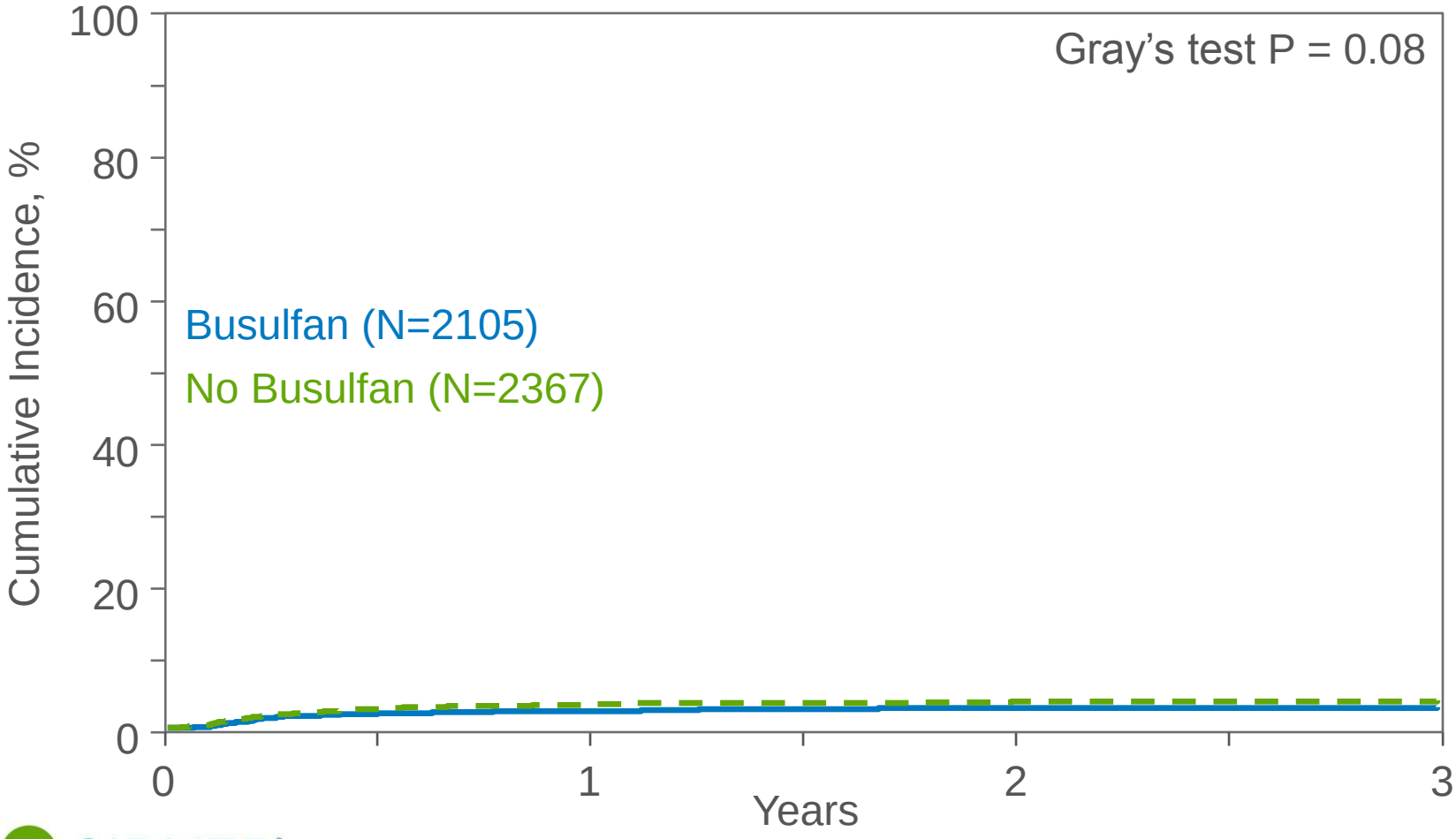
Year of HCT: 2008-2012

Incidence of TA-TMA by Busulfan Use Myeloablative Conditioning Regimens Only



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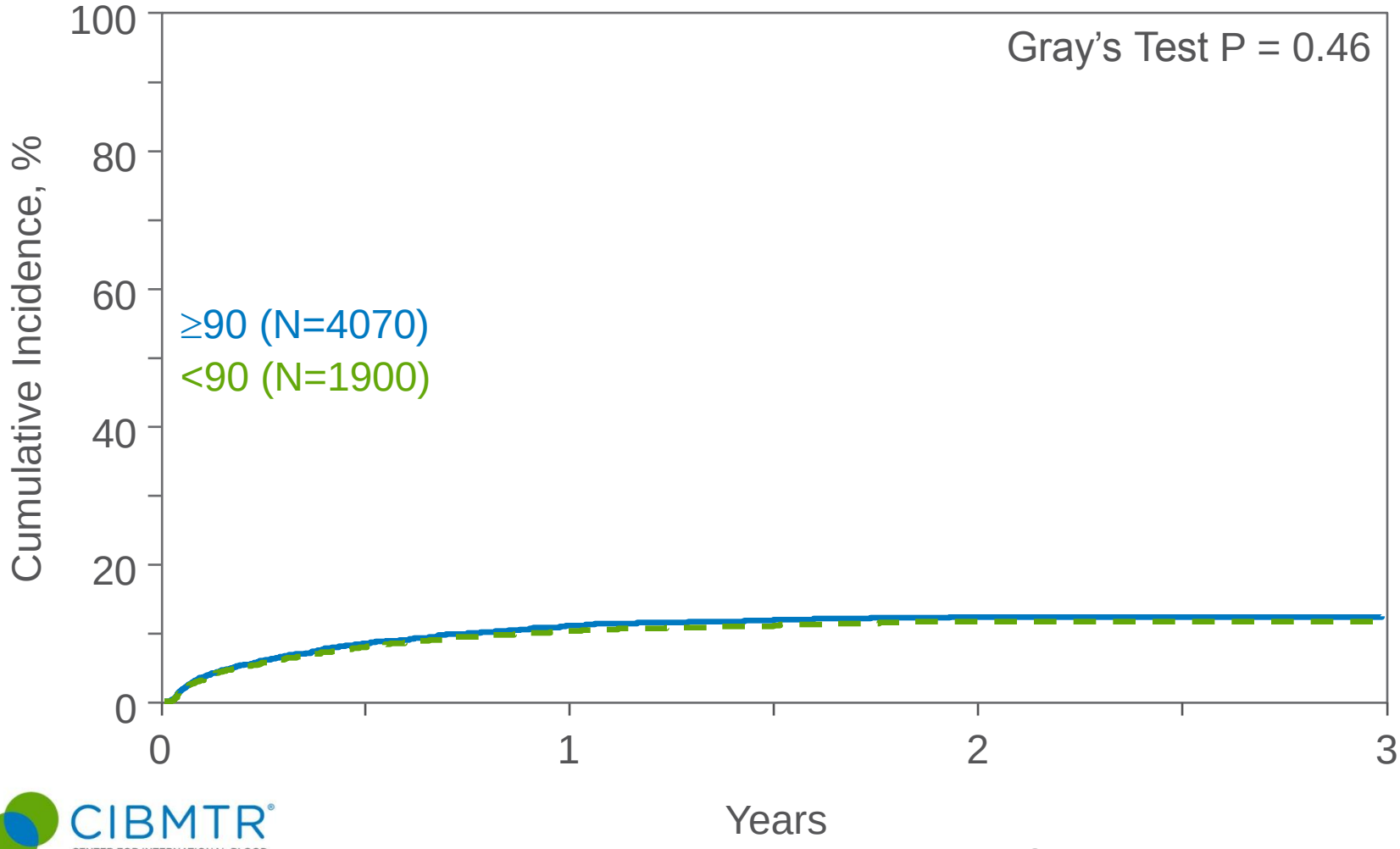
Year of HCT: 2008-2012

Incidence of IPn/Pulmonary Hemmorhage by KPS at HCT



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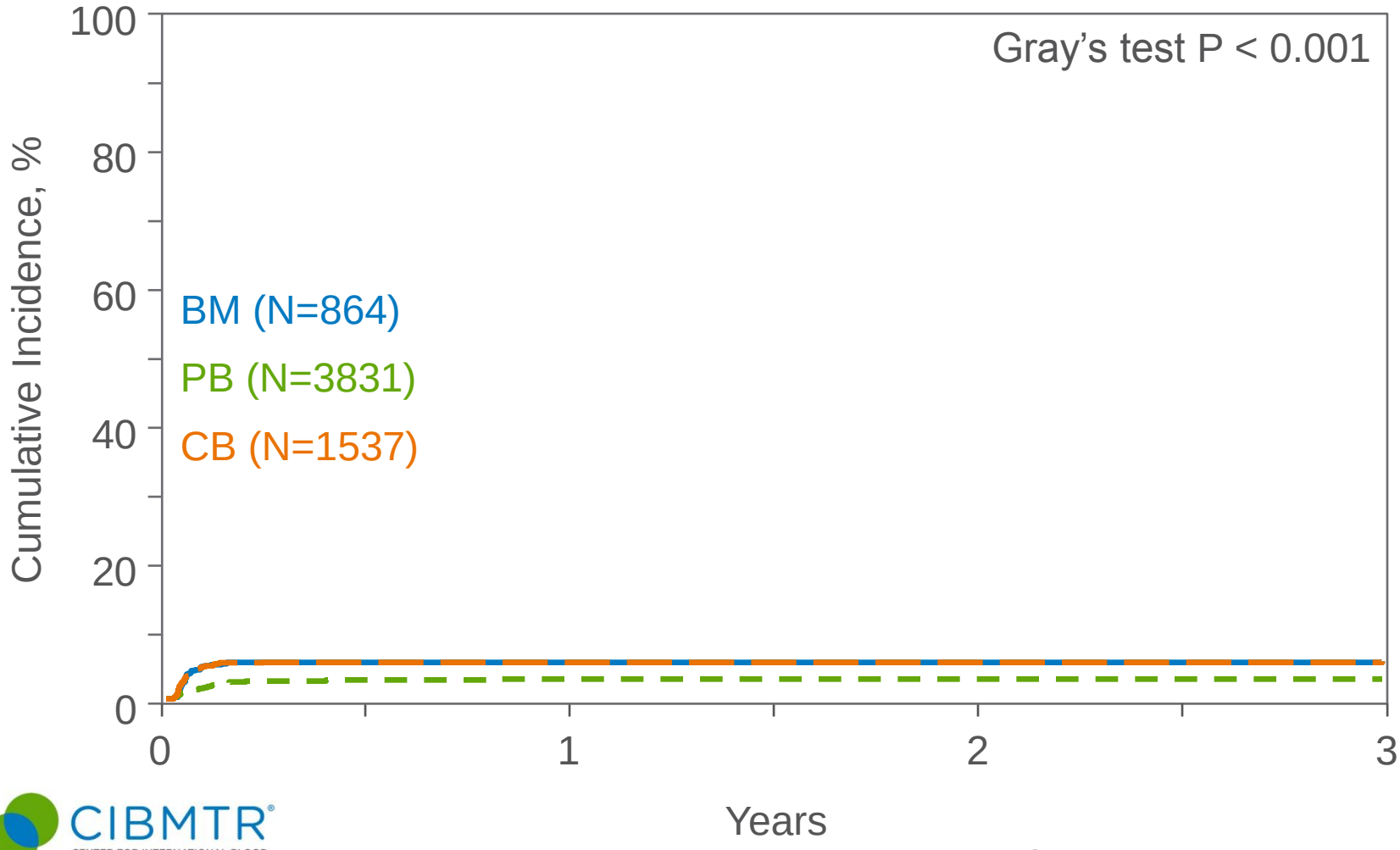
Year of HCT: 2008-2012

Incidence of Veno-Occlusive Disease by Graft Source



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Year of HCT: 2008-2012

Patients

	SIR+VOD+	SIR+VOD-	SIR-VOD+	SIR-VOD-
Sample Size	13	26	9	15
Age, median (range)	45 (19-59)	42.5 (29-56)	34 (19-51)	48.5 (31-58)
Gender, male (%)	69	31	33	80
Donor Type				
Matched Related (%)	15	85	33	60
Matched Unrelated (%)	77	15	67	33
Time to neutrophil recovery Median (range)	14 (10-20)	13 (10-21)	17.5 (13-27)	16 (13-20)
Time to platelet recovery Median (range)	29 (14-138)	15 (8-39)	20 (15-102)	18 (14-26)
Acute GVHD (%)				
Grade 0 - I	69	69	53	44
Grade II - IV	23	31	40	56

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*Cutler C, et al. BBMT 2010. 16 (8): 1180-1185

Are there situations in which corticosteroids alone are sufficient to treat IPS

- **After reduced intensity (RIC) regimen?**

  High response rates to steroids alone (71%) if post-RIC.

- **Early in the course of IPS (lower FiO2 levels)?**

  High response rate to steroids alone (91%) if FiO2 $\leq$ 40%

  Low response rates to steroids alone (17%) if FiO2 > 40%

Table I. Clinical criteria for veno-occlusive disease.

Modified seattle criteria (Shulman & Hinterberger, 1992)	Baltimore criteria (Jones *et al*, 1987)
Two of the following criteria must be present within 20 d of transplant:	Bilirubin must be >34·2 μmol/l (2 mg/dl) within 21 d of transplant and two of the following criteria must be present:
Bilirubin >34·2 μmol/l (2 mg/dl)	Hepatomegaly
Hepatomegaly or right upper quadrant pain	Ascites
Weight gain (>2% from pre-transplant weight)	Weight gain (>5% from pre-transplant weight)

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*Dignan FL, et al. BJH 2013. 163: 444-457
*Shulman HM & Hinterberger W. BMT 1992. 10: 197-214
*Jones RJ, et al. Transplantation 1987. 44: 778-783

Modeling

Time	Biomarker	OR** (95% CI)	p **
Day -1	vWF>=1200 mU/mL	2.57 (1.27 - inf)	0.009
Day +7	vWF>=1400 mU/mL	2.35 (1.23 - inf)	0.01
	TM>=100 ng/mL	2.35 (1.23 - inf)	0.01
	sICAM1>=400 ng/mL	3.04 (1.25 - inf)	0.01

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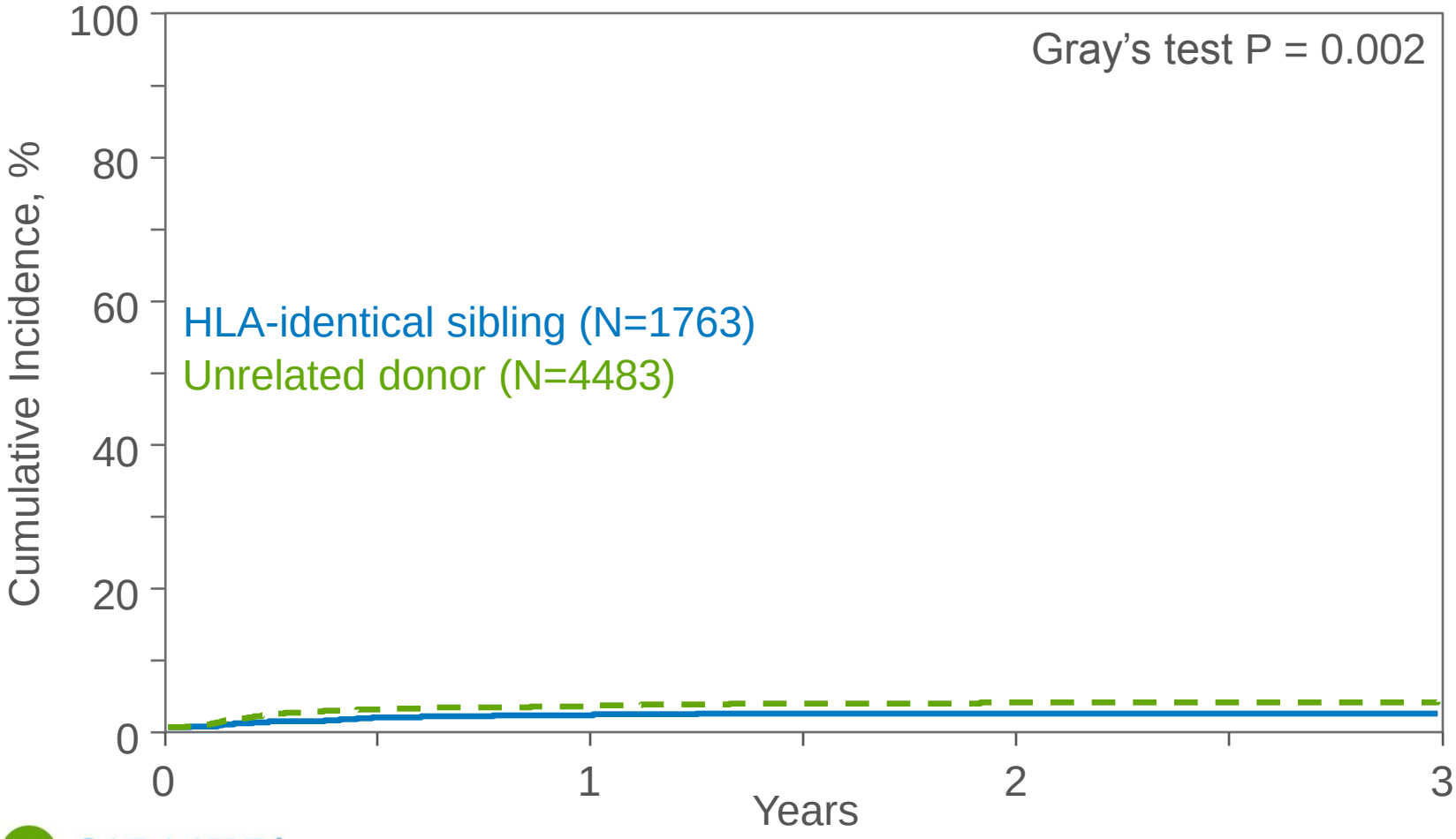
*Cutler C, et al. BBMT 2010. 16 (8): 1180-1185

Incidence of TA-TMA by Donor Type



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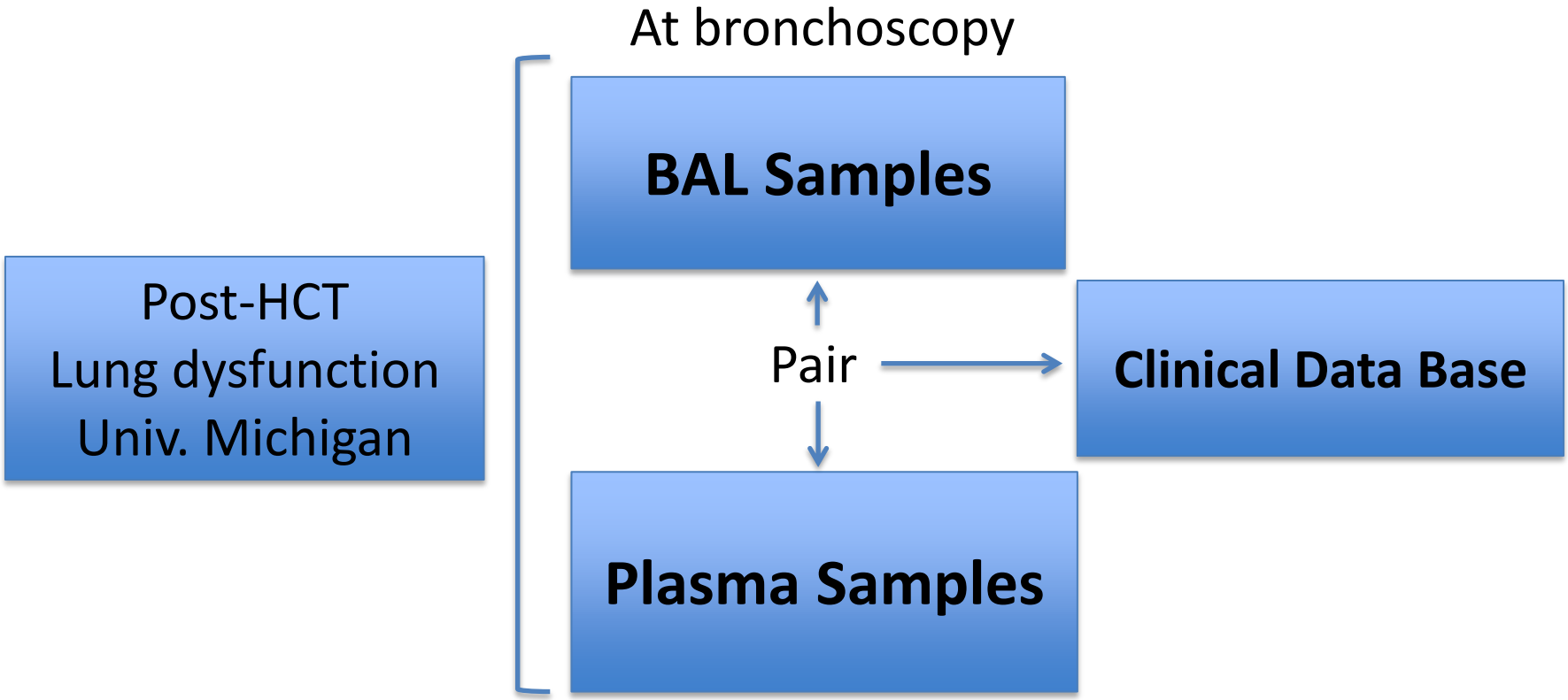
Year of HCT: 2008-2012

Biomarkers in Lung Injury post-HCT
Pulmonary Biorepository at Univ Michigan



Demographics: BMT CTN 0403

Factor		Etanercept (%) n= 16	Placebo (%) n = 18
Gender	Male	8 (50)	8 (44)
	Female	8 (50)	10 (56)
Age (yrs)			
	Median	47.7	46.4
	Mean	47.9	47.8
	SD	± 14.4	± 11.6
Disease			
	AML/MDS	3 (18)	11 (61%)
	ALL	3 (18)	4 (22)
	NHL	3 (18)	0 (0)
	Other	6 (38)	2 (11)

Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic HCT

BMT CTN 1202

John Levine, Co-Chair

John Hansen, Co-Chair