

NIH Criteria for Chronic GVHD

- Historical overview
- Rationale for new criteria
- Definitions
- Validation studies
- Perspective

Chronic GVHD: Overview

- Pleiomorphic syndrome affecting multiple organs
- Onset at 3 – 28 months after transplant
- 40 – 60% incidence among 3-month survivors
- Immune dysfunction with risk of infections
- Requires prolonged immunosuppressive treatment
- 30-50% risk of transplant-related mortality
- Associated with reduced risk of relapse

Historical Changes in Nomenclature

- **Early 1970's:** Small case series of “late” GVHD
- **Late 1970's:** Skin manifestations >150 days noted as different from acute GVHD; termed as “chronic” GVHD
- **1980:** Original chronic GVHD classification into “Limited” and “Extensive” categories
- **2001:** Seattle categories revised according to need for systemic treatment
- **2004:** NIH consensus criteria for clinical trials

What does “Chronic” mean?

- Begins later than acute GVHD
- Lasts longer than acute GVHD
- Looks different from acute GVHD

Original Classification of Chronic GVHD

Limited

- Localized skin involvement or
- Hepatic dysfunction due to chronic GVHD, or
- Localized skin involvement and hepatic dysfunction

Extensive

- Generalized skin involvement, or
- Findings of limited chronic GVHD plus
 - Aggressive hepatitis, bridging necrosis, cirrhosis, or
 - Ocular sicca, or
 - Oral involvement, or
 - Involvement of any other organ

Problems with the Original Classification

- Based on limited experience (n = 20)
- Cases that did not fit either category
 - Ocular and oral involvement without skin findings
 - Severe liver disease without skin involvement
- Poorly defined boundary between localized and generalized skin involvement
- Cases that completely mimic acute GVHD
 - With onset, recurrence or persistence at >100 days
 - Especially after reduced intensity conditioning

2001 Seattle Classification

Indications for systemic immunosuppressive treatment

- More than mild abnormalities involving a single site, or
- Involvement of multiple sites, or
- Characteristics indicating mortality risk
 - Platelet count $<100,000/\mu\text{L}$ at chronic GVHD onset, or
 - Steroid treatment at the onset of chronic GVHD

2004 NIH Consensus Criteria

- Establish new criteria for use in chronic GVHD clinical trials
- Goals:
 - Criteria for diagnosis
 - Organ scoring system
 - Overall severity categories
 - Indications for treatment
- Based on expert opinion

NIH Consensus Criteria: Diagnosis

- One diagnostic manifestation (with or without biopsy), or
- One distinctive manifestation, confirmed by biopsy or other relevant test in the same organ or a different organ
- Exclusion of other causes (e.g., infection)

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Chronic GVHD: Diagnostic Manifestations

- Skin poikiloderma, lichen planus, sclerotic or morphea features, lichen sclerosus
- Mouth lichen-type features, hyperkeratotic plaques, sclerotic restriction of oral opening
- GI tract esophageal web, upper esophageal strictures or stenosis
- Other biopsy-proven bronchiolitis obliterans, fasciitis, joint sclerosis, vulvo-vaginal lichen planus, scarring or stenosis

Chronic GVHD: Distinctive Manifestations

- Skin depigmentation, nail changes, alopecia
- Mouth xerostomia, mucocele, mucosal atrophy, pseudomembranes, ulcers
- Eyes sicca, cicatricial conjunctivitis, keratoconjunctivitis sicca, confluent punctate keratopathy
- Genitalia erosions, fissures, ulcers
- Other bronchiolitis obliterans diagnosed without biopsy, myositis

Overlap Manifestations: Acute and Chronic GVHD

- Skin erythematous rash, pruritis, exfoliation
- Mouth mucositis, erythema, gingivitis, pain
- Liver abnormal liver function tests
- GI tract anorexia, nausea, vomiting, diarrhea, malabsorption

Chronic GVHD: Other Manifestations

- Skin anhidrosis, ichthyosis, pigment changes, hair thinning, premature gray hair
- Eyes photophobia, periorbital hyperpigmentation, blepharitis
- GI pancreatic exocrine insufficiency
- Other edema, cramps, arthralgia, effusions, neuropathy, nephrotic syndrome, myasthenia gravis, thrombocytopenia, eosinophilia, lymphopenia, hypo or hypergammaglobulinemia, autoantibodies

GVHD Categories

Acute GVHD*

- Classic acute GVHD (onset before day 100)
- Persistent, recurrent, or late-onset acute GVHD

NIH Chronic GVHD

- Classic chronic GVHD
- Overlap syndrome

*features of chronic GVHD are absent

Distinction between Acute and Chronic GVHD

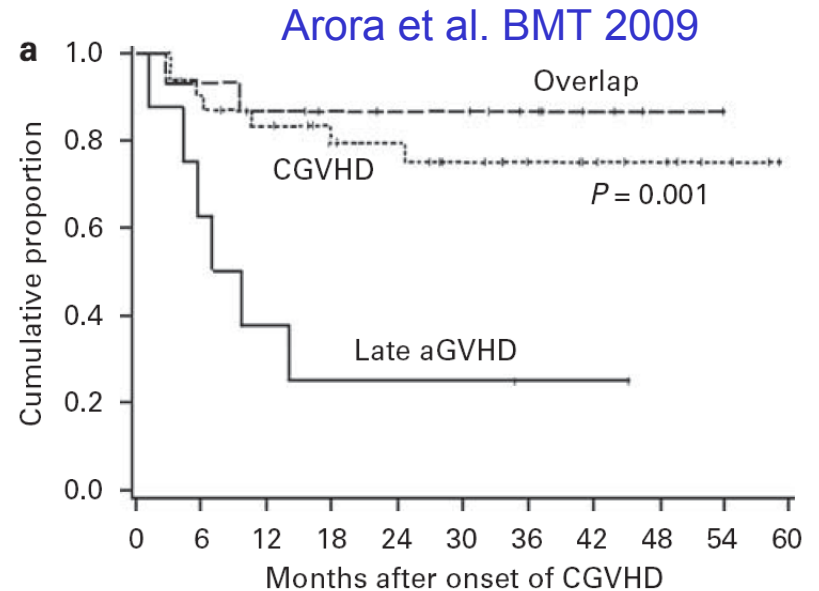
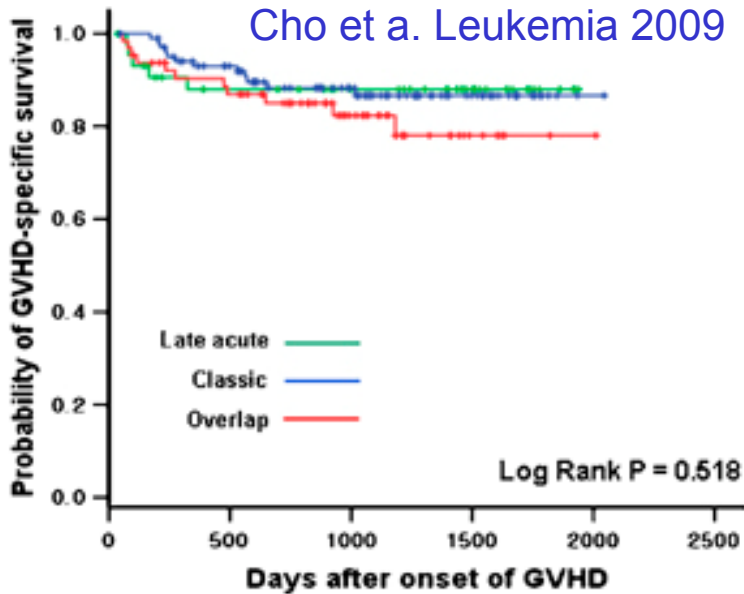
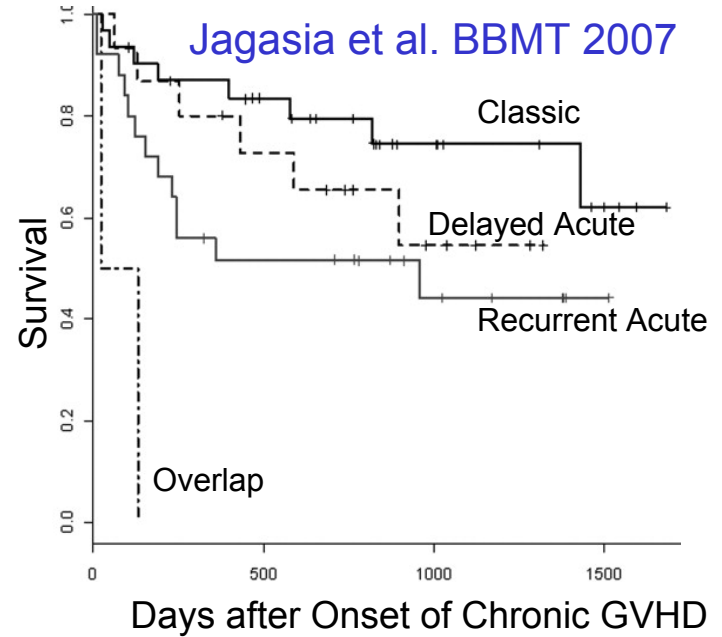
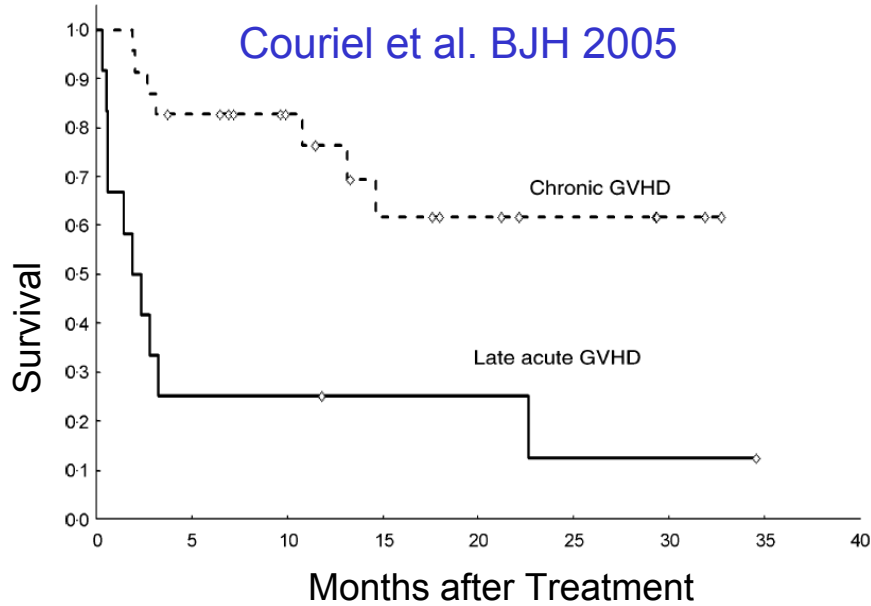
Contrary to the “day 100 myth”....

- Overlap manifestations can begin before or after day 100
- Diagnostic or distinctive manifestations of chronic GVHD can begin before or after day 100

Retrospective Validation of NIH Criteria

- Does the distinction between late acute and NIH chronic GVHD predict outcome?
- Does the distinction between NIH classic chronic GVHD vs. overlap syndrome predict outcome?
- Outcomes
 - Overall mortality
 - Non-relapse mortality
 - Recurrent malignancy
 - End of systemic treatment

Correlation with Survival?



Seattle Review

- 740 previously reported patients with chronic GVHD after myeloablative HCT between 1994 and 2000
- 48% (352/740) did not meet NIH consensus criteria at onset
- 28% (100/352) of patients with “late acute” GVHD at onset subsequently developed manifestations that met NIH criteria for chronic GVHD

Major Outcomes: NIH chronic vs. Late Acute GVHD

Outcome	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Nonrelapse mortality	1.02 (0.8-1.3)	0.87 (0.6-1.2)
Recurrent malignancy	0.76 (0.6-1.1)	0.98 (0.7-1.5)
Overall mortality	0.92 (0.7-1.1)	0.84 (0.6-1.1)
Discontinued systemic treatment	0.91 (0.7-1.1)	1.09 (0.8-1.4)

NIH chronic and late acute GVHD categories fixed at onset

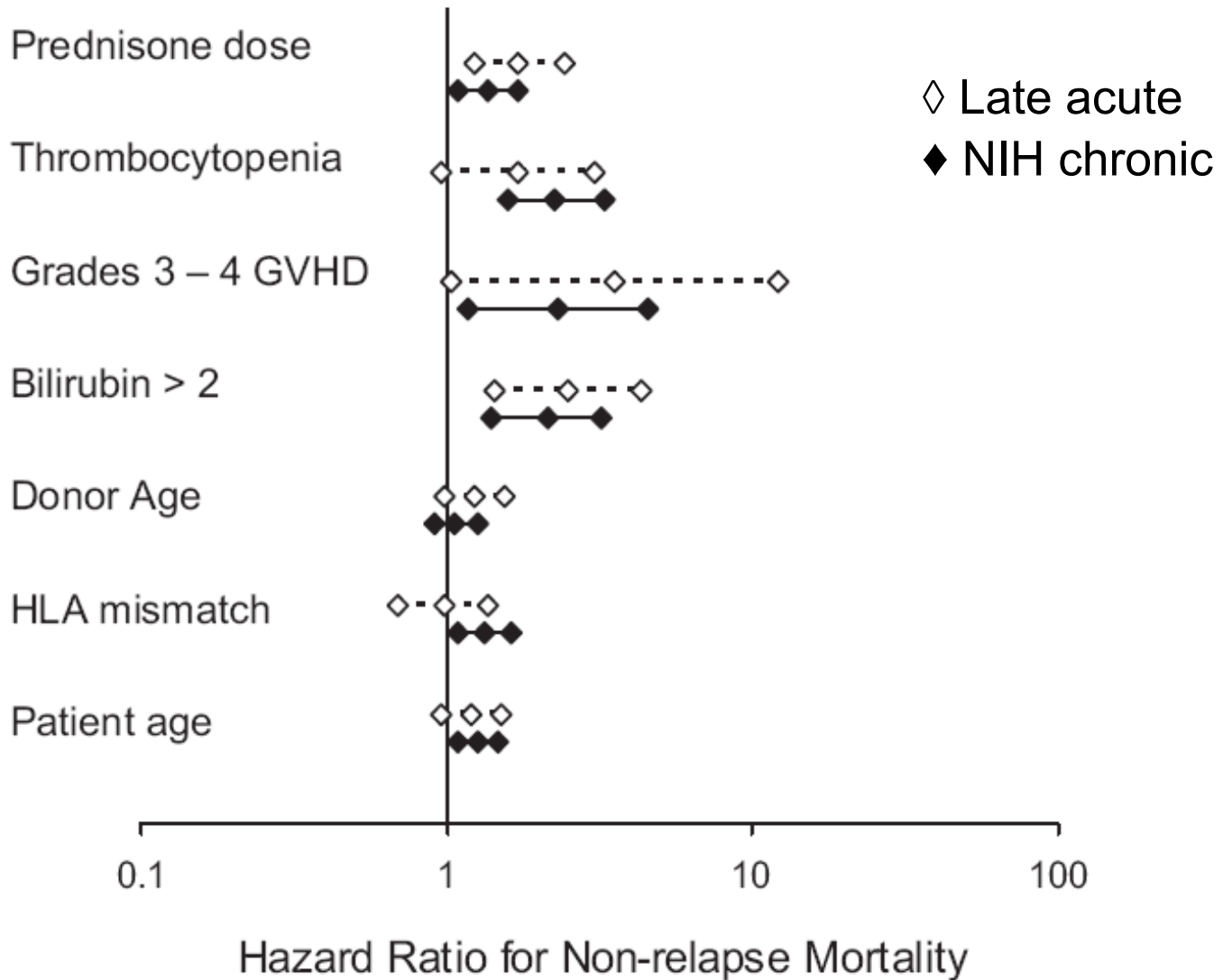
*Adjusted for onset type, prednisone dose at onset, platelet count at onset, prior acute GVHD, patient and donor age, HLA mismatch, female donor for male patient, type of graft, transplant year, and number of organs affected by chronic GVHD

Major Outcomes: NIH chronic vs. Late Acute

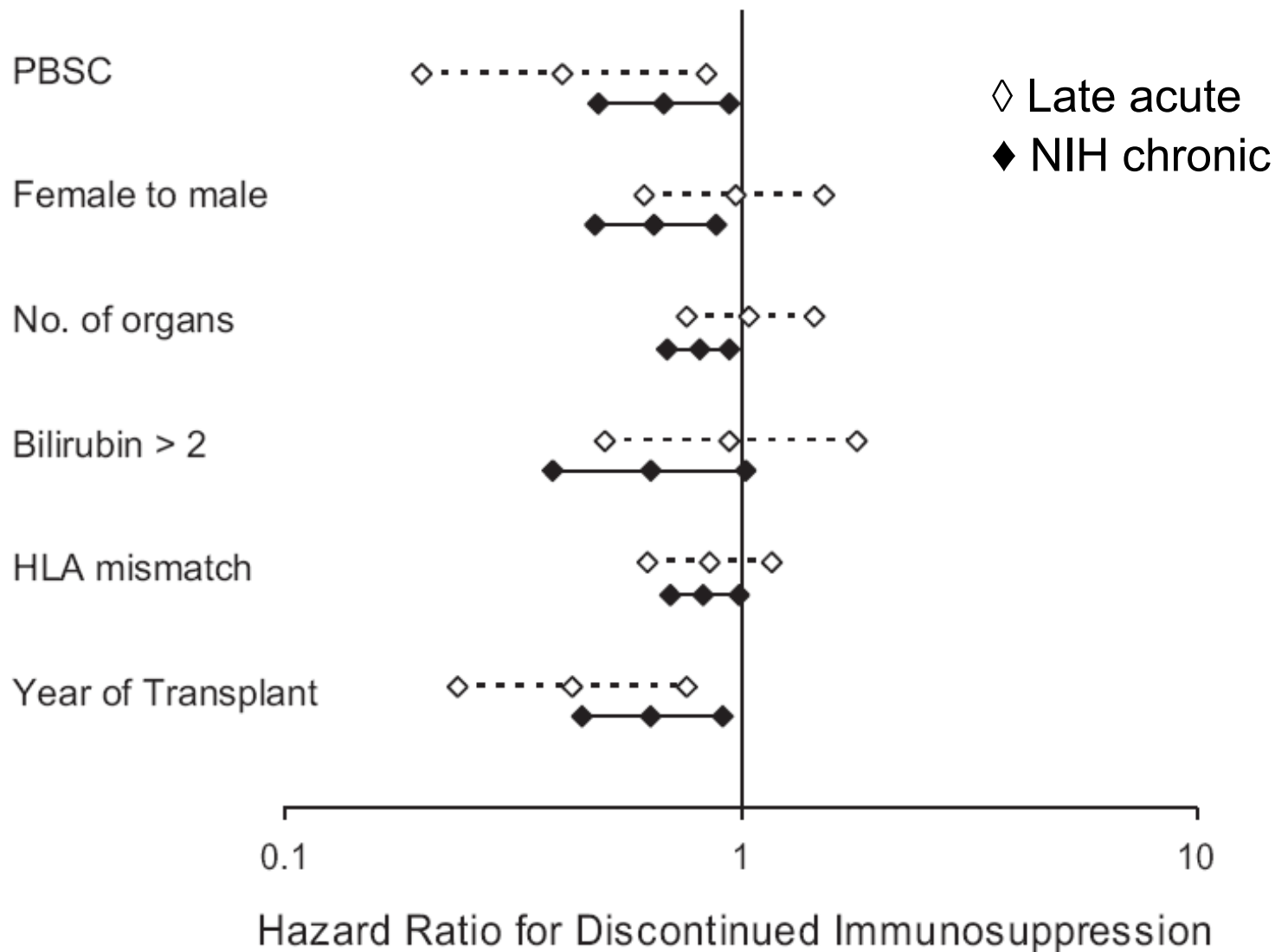
Outcome	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Nonrelapse mortality	1.23 (0.9-1.7)	1.02 (0.7-1.5)
Recurrent malignancy	0.74 (0.5-1.0)	0.94 (0.6-1.4)
Overall mortality	1.01 (0.8-1.3)	0.90 (0.7-1.2)
Discontinued systemic treatment	0.60 (0.5-0.8)	0.76 (0.6-1.0)

Transition from late acute to NIH chronic treated as competing risk

Similarity in Risk Factors for NRM



Similarity in Risk Factors for End of Treatment



Reasons for Discrepant Results

- Differences in historical criteria for diagnosis of chronic GVHD in each center
- Inadequacies of medical records in documenting the presence or absence of diagnostic or distinctive manifestations of chronic GVHD according to NIH criteria

Implications

- Patients with late acute GVHD and NIH chronic GVHD can be enrolled together in clinical trials
- Caveats:
 - Retrospective comparisons in 3 of the 4 studies
 - Response rates have been analyzed in only one study (Couriel et al. BJH 2005)
- Stratification for late acute GVHD and NIH chronic GVHD is needed until prospective studies have confirmed the absence of differences in outcomes

NIH Criteria: Organ Severity

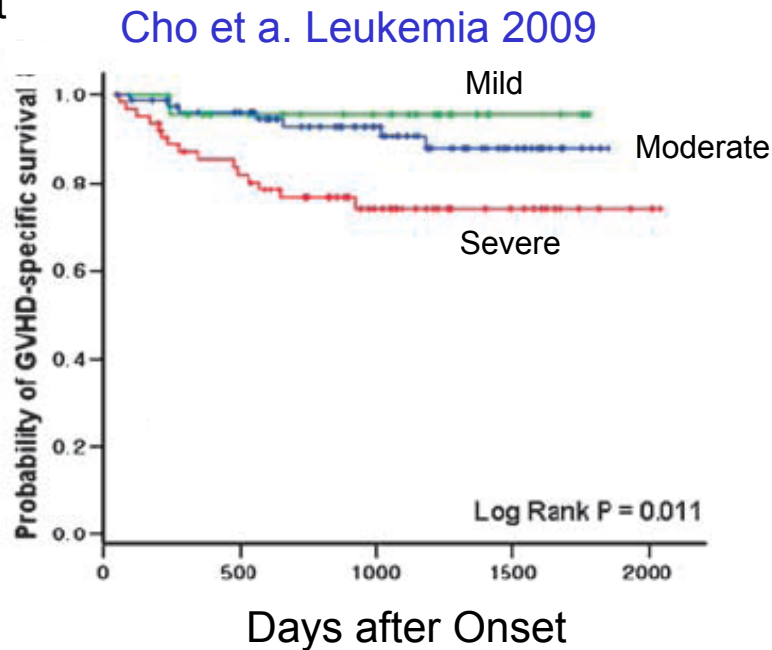
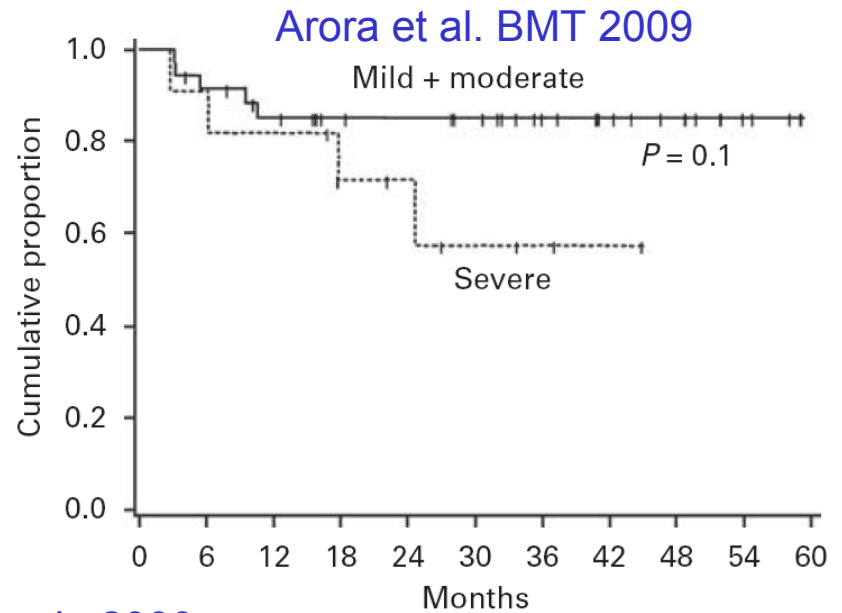
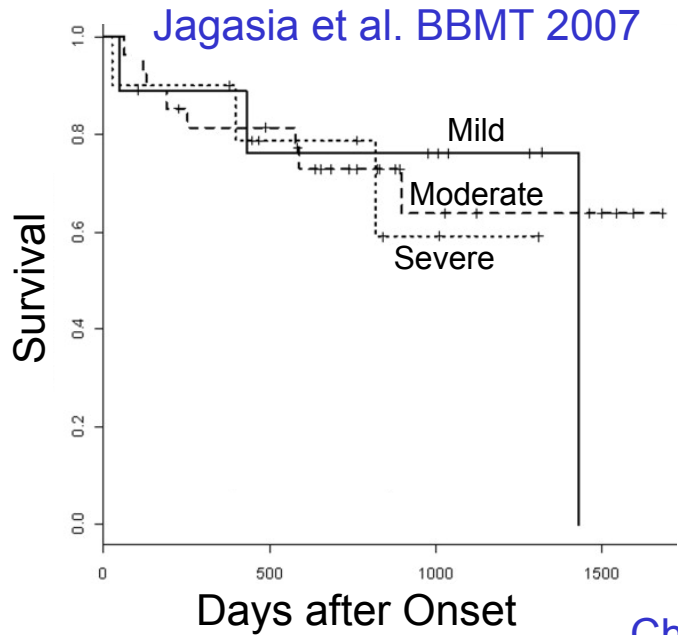
- 0 – no clinical manifestations
- 1 – clinical manifestations with no more than mild disability
- 2 – clinical manifestations with moderate disability
- 3 – clinical manifestations with severe disability

Proposed New Categorization

Category	Number of Organs	Maximum Severity
Mild*	≤ 2	1 (0 for lung)
Moderate (a)	≥ 3	1 (0 for lung)
Moderate (b)	any	2 (1 for lung)
Severe	any	3 (2 for lung)

*Systemic treatment generally not necessary; topical therapy often sufficient

Severity at Onset Correlated with Survival?



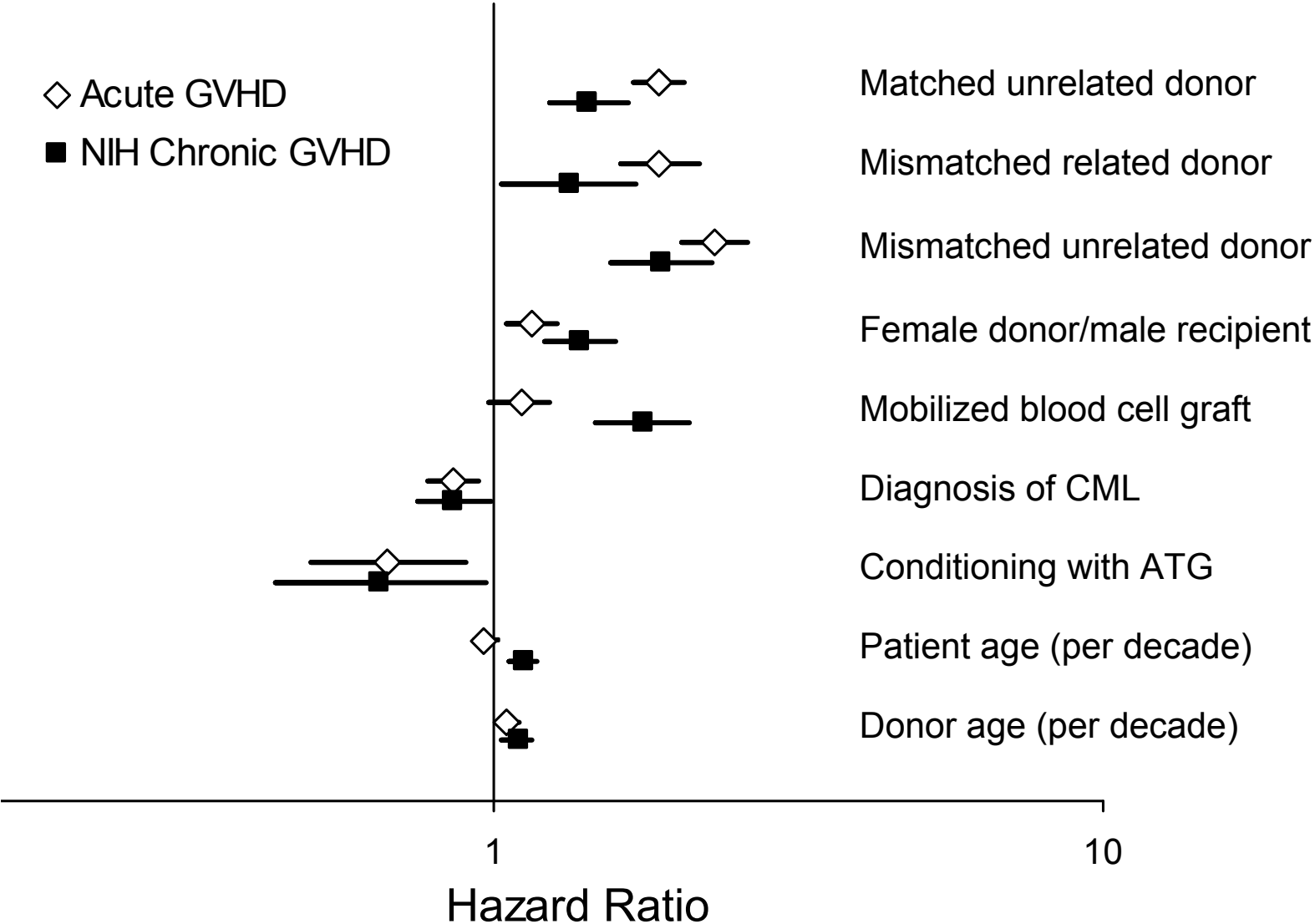
A Single Pathway for Acute and Chronic GVHD?

- Compared risk factors for grades 2-4 acute GVHD and NIH chronic GVHD
- Similarity of risk factors would suggest similarity in pathogenic pathways
- Major differences in risk factors would suggest differences in pathogenic pathways

Cohort and Approach

- 2941 patients, July 1992 – December 2005
 - Hematologic malignancy
 - First allogeneic transplant with myeloablative conditioning
 - Related or unrelated donor
 - Marrow or growth-factor mobilized blood cell grafts
 - Overlap syndrome analyzed as both acute and chronic GVHD
- Grades II – IV GVHD before or after day 100
 - 80% cumulative incidence at 6 months
- NIH chronic GVHD
 - 34% cumulative incidence at 2 years
- Both acute and NIH chronic GVHD in 31% of patients
- No GVHD in 16% of patients

Similarity in Risk Factors for Acute and Chronic



Does short-term response predict cure?

- Evaluated definitions of response at 3 and 6 months as predictors of cure within 2 years
- Response definition at 3 or 6 months strongly correlated with cure could be used as an end-point for future phase II studies

Cohort and Approach

- Patients who participated in MMF study
- Definition of “success”
 - Resolution of chronic GVHD and withdrawal of systemic immunosuppression within 2 years without secondary therapy
 - No bronchiolitis obliterans, recurrent malignancy or death during primary treatment
- Definition of “failure”
 - Secondary therapy
 - Development of bronchiolitis obliterans during primary therapy
 - Primary therapy without success for >2 years
- Compare response rates at 3 and 6 months in success and failure groups

Correlations at 3 Months

Response Definition—n (%)	Failures (n=49)	Successes (n=21)
Overall severity assessed by MD	47 (96)	19 (90)
Improved	24 (51)	11 (58)
MD assessed change from baseline	46 (94)	19 (90)
Improved	24 (52)	13 (68)
Improved number of affected sites	35 (71)	16 (76)
Improved maximum organ severity	27 (55)	10 (48)
Improved overall NIH severity	22 (45)	9 (43)
Prednisone dose, mg/kg/day—mean (SD)	0.29 (0.19)	0.17 (0.14)

Correlations at 3 Months

Response Definition—n (%)	Failures (n=49)	Successes (n=21)
Not improved in any organ	1 (2)	0 (0)
Improved in at least one organ	47 (96)	21 (100)
Improved or stable in all organs	33 (67)	14 (67)
Improved in all organs	12 (24)	6 (29)
Complete response in at least one organ	41 (84)	20 (95)
CR \geq one organ, stable or improved all others	27 (55)	14 (67)
Overall partial response	25 (51)	9 (43)
Overall complete response	8 (16)	5 (24)
Overall partial or complete response	33 (67)	14 (67)

Correlations at 6 Months

Response Definition—n (%)	Failures (n=40)	Successes (n=19)
Overall severity assessed by MD	38 (95)	17 (89)
Improved	19 (50)	11 (65)
Improved number of affected sites	24 (60)	14 (74)
Improved maximum organ severity	19 (48)	12 (63)
Improved overall NIH severity	13 (33)	11 (58)
Prednisone dose (mg/kg/day)—mean (SD)	0.16 (0.17)	0.05 (0.10)

Correlations at 6 Months

Response Definition—n (%)	Failures (n=40)	Successes (n=19)
Not improved in any organ	0 (0)	0 (0)
Improved in at least one organ	36 (90)	19 (100)
Improved or stable in all organs	21 (52)	13 (68)
Improved in all organs	8 (20)	6 (32)
Complete response in at least one organ	31 (75)	17 (89)
CR \geq one organ, stable or improved all others	19 (48)	13 (68)
Overall partial response	15 (38)	7 (37)
Overall complete response	6 (15)	6 (32)
Overall partial or complete response	21 (53)	13 (68)

Interpretation

- Short-term response is not strongly associated with cure of chronic GVHD
- Short-term response measures anti-inflammatory and immunosuppressive effects
- Cure measures development of tolerance
- Tolerance is not necessarily accelerated by anti-inflammatory and immunosuppressive treatment

Perspective

- NIH criteria have helped to “standardize” terminology
- Retrospective studies show inconsistent results
- Late acute GVHD and NIH chronic GVHD show
 - Similar risk factor profile
 - Similar clinical outcomes
- “Overlap” syndrome has unknown validity and significance as a subcategory of NIH chronic GVHD
- Response and tolerance should be distinguished from each other in clinical trials
- Prospective studies are needed to generate data supporting validity of expert opinion in NIH criteria

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