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Systemic immune inflammation index combined with Epstein–Barr virus DNA for predicting the prognosis of nasopharyngeal carcinoma: A retrospective study

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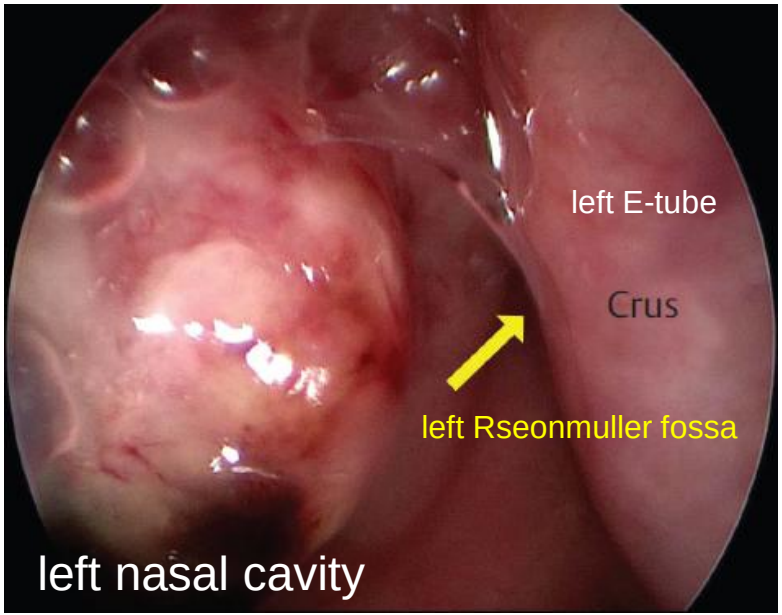
Nasopharyngeal carcinoma

- undifferentiated form of squamous cell carcinoma
- often arising from Rosenmuller fossa
- most common malignancy in nasopharynx



Etiology & Epidemiology

- interplay of environmental factors, genetic structure, and EBV infection
  - environmental: smoking (2-6 fold), alcohol
  - genetic: Chinese
  - EBV infection, (HPV infection)
- endemic to southern China, Southeast Asia, and Africa
  - 25-50 cases per 100000 people in male, 15-20 cases per 100000 people in female
  - 1 per 100000 in non-endemic region
- male predominance

Clinical presentation

- nasal symptoms:
  - **unilateral** nasal obstruction, epistaxis, post-nasal drip, hyponasal speech, cacosmia
- otological symptoms:
  - Eustachian tube obstruction
  - conductive hearing loss, middle ear effusion, aural fullness
- neurological symptoms:
  - abducens nerve palsy (most common)

Diagnosis & screening

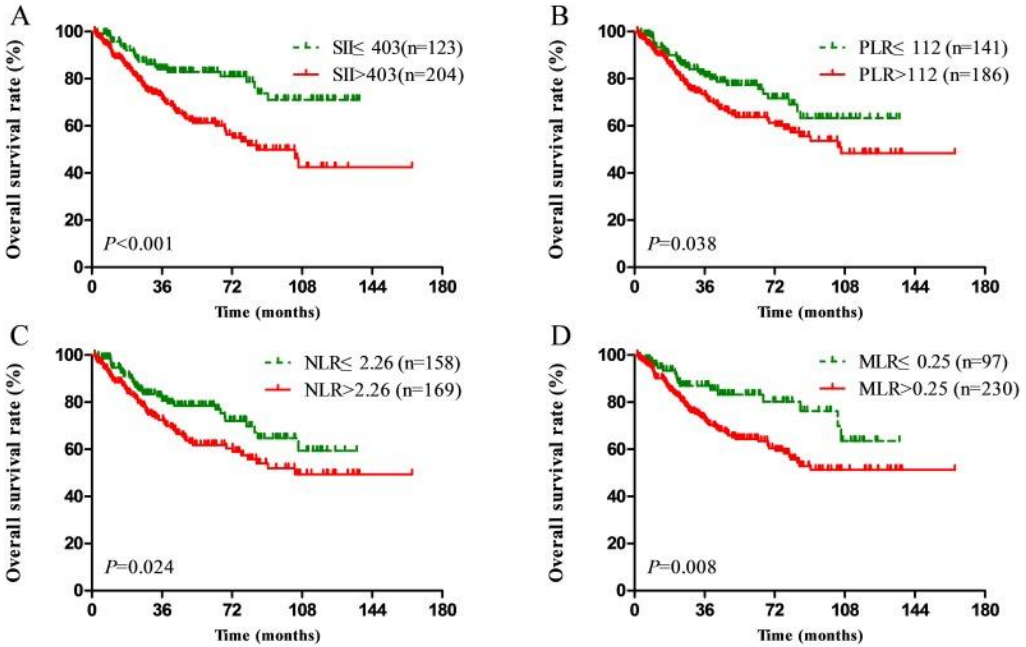
- definite diagnosis: endoscopic-guided biopsy
  - EBV DNA in plasma or serum
  - EBV-encoded small RNA in biopsy

- screening:
  - plasma EBV DNA
  - anti-EBV IgA antibodies (early antigen (EA)-IgA, VCA-IgA, EBV nuclear antigen 1 (EBNA1)-IgA)
  - endocopy and MRI

Annals of Oncology, Volume 32, Issue 4, 452 - 465

Prognostic indicator

- **golden standard: TNM staging**
- serum EBV viral load
- EBV DNA
- systemic inflammatory factors (SII, PLR, NLR, MLR)

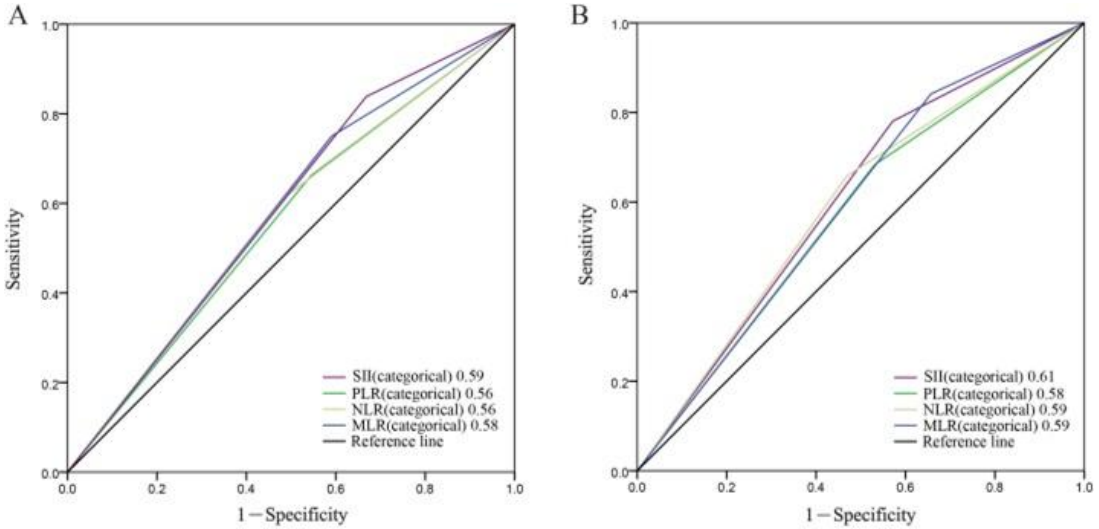


High SII, PLR, NLR and MLR scores were associated with poor OS

Oncotarget. 2017 Aug 2;8(39):66075–66086.

Systemic inflammatory index

- SII = (Platelet Count × Neutrophil Count) / Lymphocyte Count



the AUC value of SII (categorical) was significantly higher

Predictive ability of the SII (categorical) was compared with PLR, NLR and MLR by ROC curves in 3-years and 5-years

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Systemic inflammatory index

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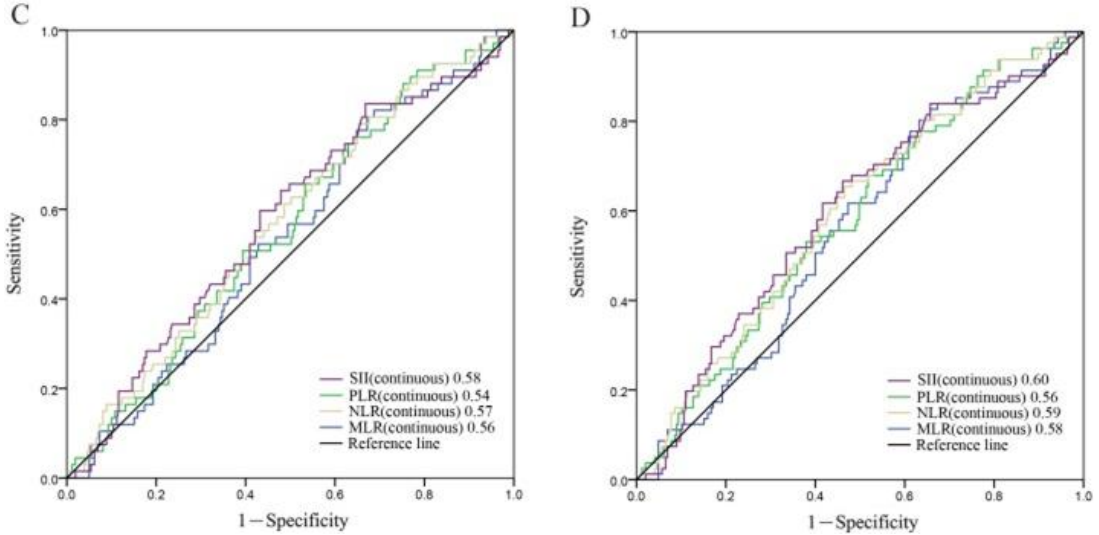
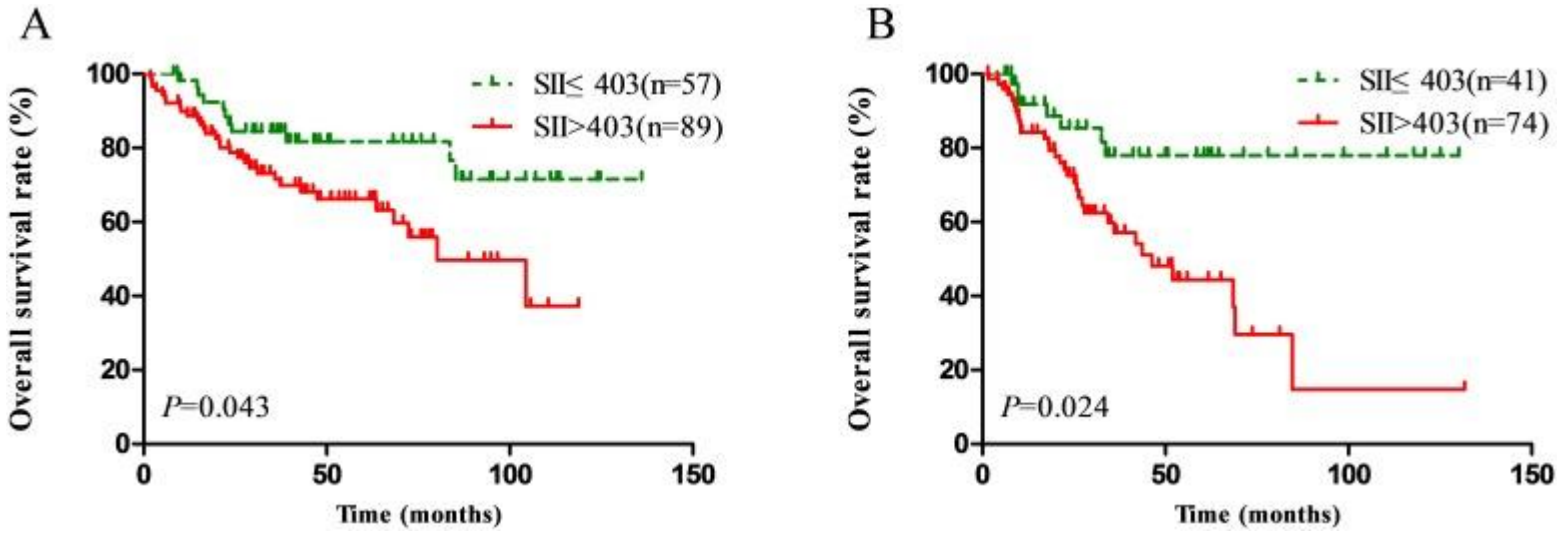


the AUC value of SII (continuous) was still significantly higher

Predictive ability of the SII (continuous) was compared with PLR, NLR and MLR by ROC curves in 3-years and 5-years

Oncotarget. 2017 Aug 2;8(39):66075–66086.

Systemic inflammatory index



in III and IV patients, high SII scores was significantly associated with poor OS

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Aim

Systemic immune inflammation index combined with Epstein–Barr virus DNA for predicting the prognosis of nasopharyngeal carcinoma: A retrospective study

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combine systemic inflammation index and EBV virus load in patients with stage I to IV NPC
compare with different inflammatory factor models
⇒ determine the best predictive model

Materials

- inclusion:
  - ≥ 18 y/o
  - pathologically confirmed NPC
  - treated at FEMH
- exclusion:
  - < 18 y/o
  - lack of hospitalization record
  - tranfer to other hospital

- 357 patients were reviewed
- 240 were analyzed
- from Jan 2016 to July 2023

Statistical Analysis

- overall survival (OS):
  - time from diagnosis to death (any cause) or last follow-up
- cut-off determination:
  - optimal thresholds for predictors identified using ROC analysis
- statistical test:
  - Continuous variables: t-tests
  - Survival impact: Univariate Cox regression
  - Significant variables re-tested in multivariate Cox models
- model evaluation:
  - Likelihood ratio chi-square (LR χ^2): assessed model discrimination
  - Higher LR χ^2 = better predictive ability
- software: STATA v14.0

Table 1
Characteristics of the recruited nasopharyngeal cancer patients ($n = 240$).

Item		N%/mean ± SD
Sex	Male	183 (76 %)
	Female	57 (24 %)
Age		53.12 ± 11.20 (20–79)
T	1	109 (45 %)
	2	50 (21 %)
	3	44 (18 %)
	4	37 (16 %)
N	0	20 (8 %)
	1	68 (29 %)
	2	87 (36 %)
	3	65 (27 %)
M	0	223 (93 %)
	1	17 (7 %)
Stage	I	11 (5 %)
	II	55 (23 %)
	III	87 (36 %)
	IVA	59 (24 %)
	IVB	26 (11 %)
	IVC	2 (1 %)
Treatment	Definitive CCRT	194 (81 %)
	Induction+ CCRT	46 (19 %)
EBV virus load	>35	88 (37 %)
	<35 & Undetected	152 (63 %)
PLR		158.6 ± 81.5 (27.9–622.9)
LMR		2.95 ± 2.34 (0–15.6)
NLR		3.40 ± 3.26 (0.75–29)
SIRI		2.55 ± 1.96 (0–18.6)
SII		880.7 ± 804.5 (155.5–6325.4)

predominance in male

optimal cutoff

EBV viral load > 35

NLR ≥ 3

PLR ≥ 103

LMR ≥ 3.6

SII ≥ 545

SIRI ≥ 2.5

Table 2
Comparisons of the severity of NPC according to different inflammatory factors.

	Stage I & II	Stage III & IV	p value
EBV Virus load			
EBV DNA <35 & Undetected	52 (79 %)	100 (57 %)	**0.002**
EBV DNA >35	14 (21 %)	74 (43 %)	
NLR			
<3	42 (67 %)	99 (59 %)	0.262
≥3	21 (33 %)	70 (41 %)	
PLR			
<103	19 (30 %)	39 (23 %)	0.268
≥103	44 (70 %)	130 (77 %)	
SIRI			
SIRI < 2.5	39 (74 %)	89 (57 %)	**0.029**
SIRI ≥ 2.5	14 (26 %)	68 (43 %)	
SII			
SII < 545	33 (52 %)	62 (37 %)	**0.031**
SII ≥ 545	30 (48 %)	107 (63 %)	

EBV viral load, SIRI, SII are related to the severity of NPC

Table 3
Univariate and multivariate Cox regression analyses for OS.

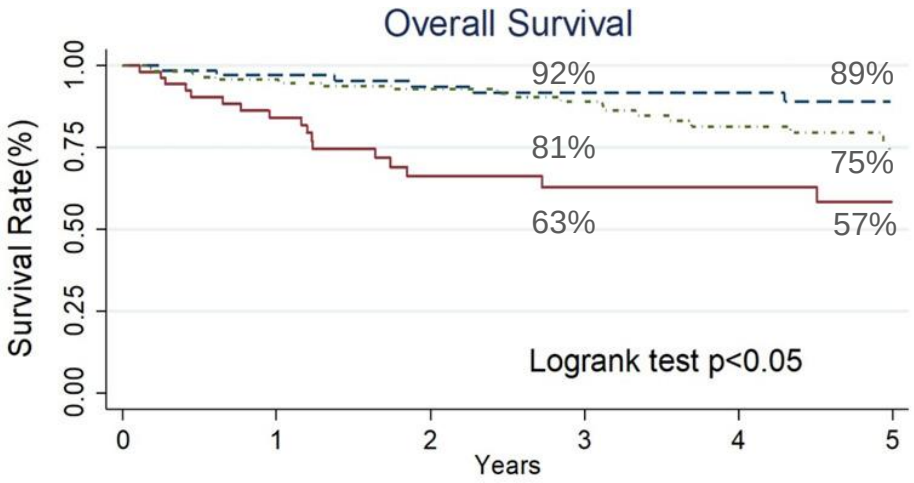
Cox-regression	Univariate		Multivariate	
	HR (95 % CI)	p value	HR (95 % CI)	p value
Gender				
Female	Ref.		Ref.	
Male	1.02 (0.5–2.06)	0.965	1.05 (0.52–2.15)	0.887
Age (Y)	1.02 (0.99–1.05)	0.095	1.03 (1.00–1.06)	0.033
Age	Ref.			
<50	1.75 (0.9–3.4)	0.097		
>50				
Stage				
I + II	Ref.		Ref.	
III + IV	4.37 (1.56–12.22)	0.005	3.80 (1.34–10.80)	0.012
EBV viral load				
<35 & Undetected	Ref.			
>35	2.15 (1.19–3.90)	0.012		
NLR				
<3	Ref.			
≥3	2.37 (1.29–4.34)	0.005		
PLR				
<103	Ref.			
≥103	2.7 (1.06–6.87)	0.037		
LMR				
<3.6	Ref.			
≥3.6	1.57 (0.84,94)	0.154		
SIRI				
<2.5	Ref.			
≥2.5	2.02 (1.11–3.68)	0.021		
SII				
<545	Ref.			
≥545	2.45 (1.21–4.98)	0.013		
EBV_SII				
EBV < 35 & Undetected/ SII < 545	Ref.		Ref.	
EBV < 35 & Undetected/ SII ≥ 545+ EBV > 35/SII < 545	1.84 (0.78–4.36)	0.165	1.87 (0.78–4.48)	0.16
EBV > 35/SII ≥ 545	4.71 (1.95–11.41)	0.001	4.02 (1.63-9.88)	0.002

advanced-stage disease, EBV viral load >35,

NLR ≥3, PLR ≥103, SIRI ≥2.5, SII ≥545

were associated with decreased survival

Survival rate



EBV<35&Undetected/SII<545	68	61	54	44	35	23
EBV>35/SII≥545	53	39	20	17	14	8
EBV<35&Undetected/SII≥545 +EBV>35/SII<545	119	103	85	66	45	30

EBV DNA load + SII

⇒ best prognostic effect

EBV < 35 + Undetected/SII < 545

⇒ better overall survival rate

Possible predictive factors for prognosis in NPC

1. genetic mutations:
    - TP53 mutation → higher risk of treatment failure, poorer sirvival outcome
2. microRNA profiles:
    - miR-17-92 cluster and miR-20a → progression
    - miR-29 and miR-375 → disease presence and outcome
3. protein biomarkers:
    - Latent Membrane Protein 1 (LMP1): EBV-encoded oncoprotein → more aggressive disease
    - tumor marker: SCC, CEA → higher risk of recurrence
4. Nutritional Indicators:
    - Prognostic Nutritional Index (PNI), Nutritional Risk Index (NRI), and HALP score

Oral Oncology Reports, Volume 11, September 2024, 100640

Limitation

1. single institution retrospective study
    - selection bias
    - practice pattern differs in each institution
2. variation in cutoff points leads to different outcomes
    - influenced by time of data collection, different models
3. only focus on overall survival
    - definition of overall survival may be different
    - disease-specific survival or progression-free survival ⇒ more comprehensive analysis
4. discrepancy in staging
    - AJCC staging system was revisioned in 2018

9th AJCC

Table 2. Classification Criteria and Stage Grouping by the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Tumor-Node-Metastasis (TNM) System and Changes from the Eighth Edition to the Ninth Version

Stage	TNM eighth edition	TNM ninth version
T category: no change		
T1	Tumor confined to nasopharynx or extension to oropharynx and/or nasal cavity without parapharyngeal involvement	Tumor confined to nasopharynx or extension to any of the following without parapharyngeal involvement: (1) oropharynx; (2) nasal cavity (including nasal septum)
T2	Tumor with extension to parapharyngeal space and/or adjacent soft tissue involvement (medial pterygoid lateral pterygoid prevertebral muscles)	Tumor with extension to any of the following: (1) parapharyngeal space; (2) adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base cervical vertebra pterygoid structures and/or paranasal sinuses	Tumor with unequivocal infiltration into any of the following bony structures: (1) skull base (including pterygoid structures); (2) paranasal sinuses; (3) cervical vertebrae
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle	Tumor with any of the following extension/involvement: (1) intracranial extension; (2) unequivocal radiological and/or clinical involvement of cranial nerves; (3) hypopharynx; (4) orbit (including inferior orbital fissure); (5) parotid gland; (6) extensive soft tissue infiltration beyond the anterolateral surface of the lateral pterygoid muscle
N category: addition of advanced extranodal extension as N3 criterion		
N0	No regional lymph node metastasis	No tumor involvement of regional lymph node(s)
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage. Retropharyngeal (irrespective of laterality)	Tumor involvement of any of the following: (1) unilateral cervical lymph node(s); (2) unilateral or bilateral retropharyngeal lymph node(s). Tumor involvement in all of the following: (1) ≤6 cm in greatest dimension; (2) above the caudal border of cricoid cartilage; (3) without advanced extranodal extension
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension above the caudal border of cricoid cartilage	Tumor involvement of bilateral cervical lymph nodes and all of the following: (1) ≤6 cm in greatest dimension; (2) above the caudal border of cricoid cartilage; (3) without advanced extranodal extension
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension and/or extension below the caudal border of cricoid cartilage	Tumor involvement of unilateral or bilateral cervical lymph node(s) and any of the following: (1) >6 cm in greatest dimension; (2) extension below the caudal border of cricoid cartilage; (3) advanced radiologic extranodal extension with involvement of adjacent muscles, skin, and/or neurovascular bundle
M category: subdivision of M1 into M1a and M1b		
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	M1: distant metastasis; M1a: ≤3 metastatic lesions in ≥1 organs/ sites; M1b: >3 metastatic lesions in ≥1 organs/sites

9th AJCC

A A, T and N groupings, eighth edition

		T1	T2	T3	T4
M0	N0	I	II	III	IVA
	N1	II	II	III	IVA
	N2	III	III	III	IVA
	N3	IVA	IVA	IVA	IVA
M1	Any N	IVB			

B A, T and N groupings, ninth edition

		T1	T2	T3	T4
M0	N0	IA	IA	II	III
	N1	IB	IB	II	III
	N2	II	II	II	III
	N3	III	III	III	III
M1	M1a	IVA			
	M1b	IVB			