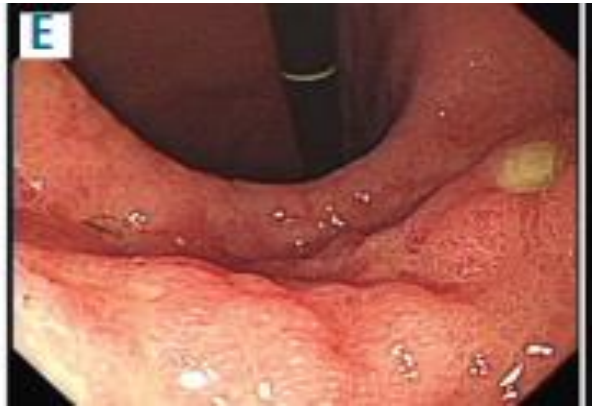
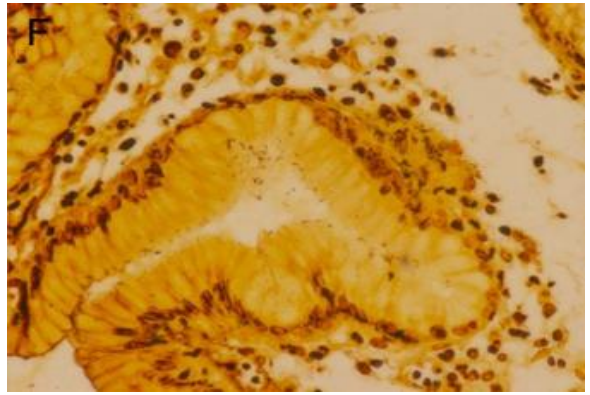




GASTRIC DIFFUSE LARGE B CELL LYMPHOMA

DR. BRADY BELTRAN GARATE

NO DISCLOUSERS

Topics

Epidemiology

Helicobacter pilori

Pathology

Clinical manifestations

Treatment

Complications

Conclusions

Epidemiology

Primary gastric lymphomas (PGLs) are a diverse group of lymphoproliferative disorders that originate from the stomach and comprise many different histologic types.

Either of diffuse large B-cell lymphoma (DLBCL) subtype or mucosa-associated lymphoma tissue (MALT) histology, PGL is the second most common gastric malignancy globally, following the adenocarcinoma of the stomach

The gastrointestinal tract (GIT) is the most common site for the development of extranodal lymphomas

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

Epidemiology

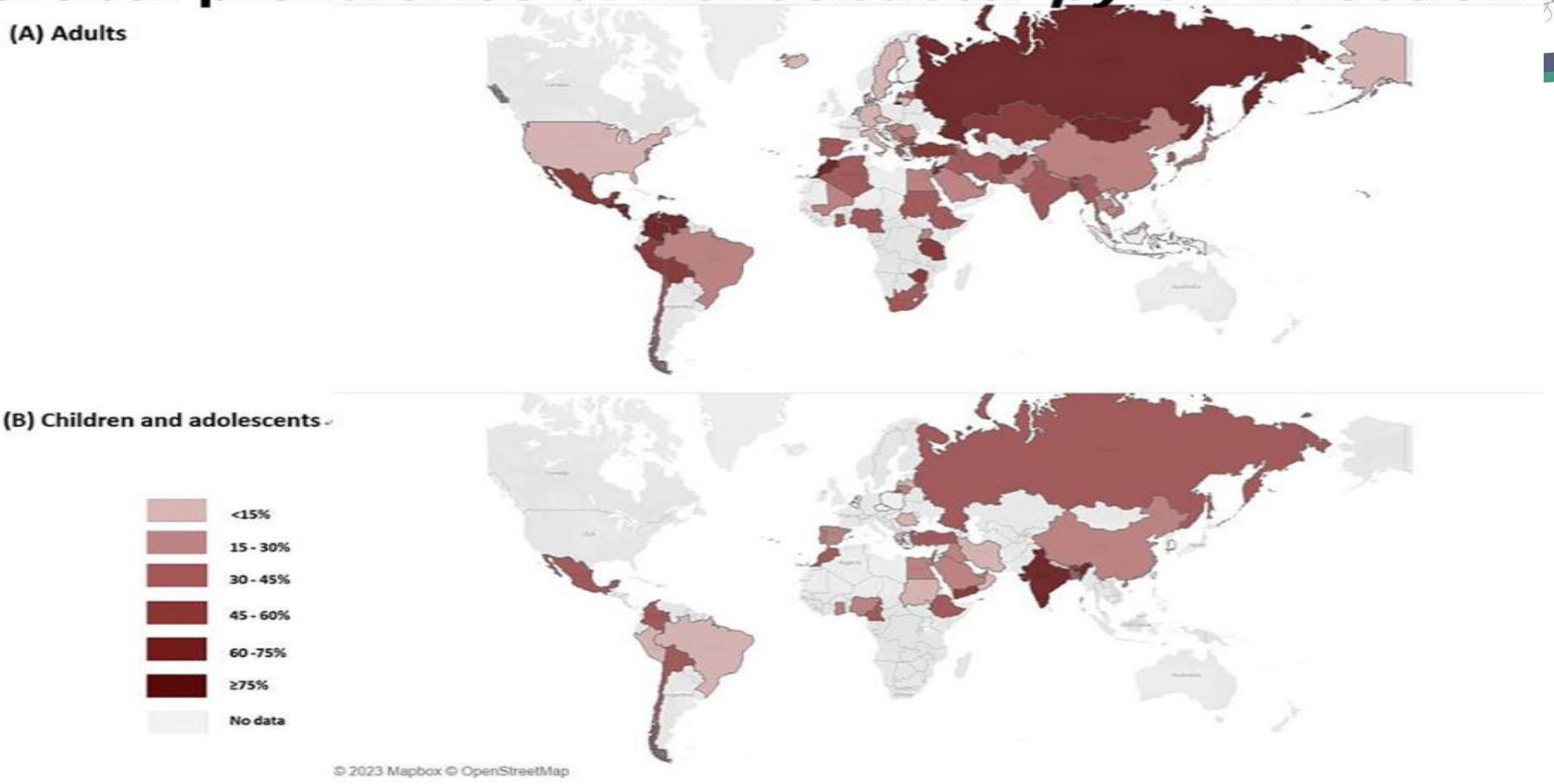
The stomach represents 30%-40% of all extranodal lymphomas and 55%-65% of all GI lymphomas.

The incidence of PGL varies from 4% to 20% of extranodal non-Hodgkin lymphomas (NHLs) and reaches up to 5% of primary gastric neoplasms.

The stomach is the most common site for the development of extranodal lymphomas in the GI tract, accounting for 60% of cases, followed by the small bowel, ileum, cecum, colon and rectum

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

Global prevalence of *Helicobacter pylori* infection



The latest (2010~2022) *H pylori* prevalence

PRIMARY GASTRIC DLBCL STAGES I/II PERUVIAN REPORT

Tabla 1. Características clínicas en los pacientes con LCGBD 1° gástrico EC I – II del HNERM diagnosticados 2010-2013 según las variables rutinarias.

	n	%
Pacientes	26	-
Edad		
Mediana (rango)	62 (30, 84)	
>60	16	61.5
Sexo Masculino	17	65.4
Escala ECOG		
0	5	19.2
1	21	80.8
Estadio clínico		
I	17	65.4
II	9	34.6
Síntomas B (+)	14	53.8

	n	%
Cirugía		
No	22	84.6
Si	4	15.4
Esquema		
R-CHOP x ≤ 3 cursos	4	15.3
R- CHOP x 4 cursos	2	7.7
R- CHOP x 5-6 cursos	10	38.4
CHOP x 6 + RT Consolid	1	3.8
R-CHOP X 4 + RT Consolid	5	19.2
R-CHOP X 6 + RT Consolid	4	15.3
Respuesta clínica		
RC	21	84.0
RP	-	
EE	1	4.0
PE	3	12.0
Desc	1	-

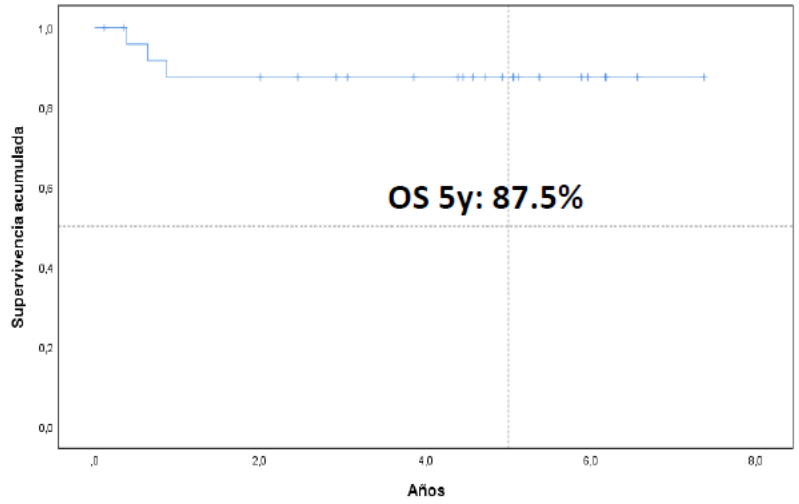


Figura 1. Supervivencia global de los pacientes con LNH DCGB 1° Gástrico EC I-II del HNERM diagnosticados 2010-2013.

Epidemiology

A Peruvian study identified that 15% of all DLBCL cases correspond to primary gastric DLBCL.

An epidemiological study in China showed that GI DLBCL may account for up to 15% of all DLBCL cases.

Peru is endemic for HP, and a recent study also shows that Peruvian HP has a high frequency of Cag A

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021
Jian Sun, Qunpei Yang, Zhaohui Lu, Miaoxia He, Li Gao, Minghua Zhu, Lu Sun, Lixin Wei, Min Li, Cuiling Liu, Jie Zheng, Weiping Liu, Gandi Li, Jie Chen, Distribution of Lymphoid Neoplasms in China: Analysis of 4,638 Cases According to the World Health Organization Classification, *American Journal of Clinical Pathology*, Volume 138, Issue 3, September 2012

DLBCL AND HELICOBACTER PILORI

H. pylori eradication can lead to complete remission in a certain fraction of patients with H. pylori-positive DLBCL (MALT).

Researchers have also found that some de novo DLBCL patients also presented complete remission after H. pylori eradication.

Furthermore, an association between H. pylori infection and de novo DLBCL was validated in a large cohort.
H. pylori-induced lymphomagenesis is a multistep process involving H. pylori virulence factors (e.g., CagA, VacA and OipA), host factors and environmental conditions.

Studies indicated that despite the carcinogenic effect of H. pylori, H. pylori infection was associated with a less aggressive subtype of de novo DLBCL,and these patients showed better prognoses.

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

DLBCL AND HELICOBACTER PILORI

Helicobacter pylori-related diffuse large B-cell lymphoma of the stomach: a distinct entity with lower aggressiveness and higher chemosensitivity

HP+ DLBCL is a distinct entity with earlier stages.

CAG-A may be responsible for direct transformation to de novo DLBCL.

The high frequency of CG DLBCL demonstrates this.

This disease has a better prognosis and greater chemosensitivity.

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021
S-H kuo et al Blood Cancer Journal 2014

DLBCL AND HELICOBACTER PILORI

Helicobacter pylori-related diffuse large B-cell lymphoma of the stomach: a distinct entity with lower aggressiveness and higher chemosensitivity

HP+ G-DLBCL vs HP- G- DLBCL has :

1.- More ulcerated lesions.
2.- Distal lesions.
3.- Early stages.
4.- No B symptoms.
5.- Normal LDH.

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021
S-H kuo et al Blood Cancer Journal 2014

HP+ GASTRIC DLBCL

It is a new entity?

- There are different clinical and endoscopic characteristics .
- There are different outcomes.
- HP+ G-DLBCL is more sensible to immunochemotherapy.
- There evidence about HP dependence (some cases responded to ATB).

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021
S-H kuo et al Blood Cancer Journal 2014

DLBCL AND HELICOBACTER PILORI

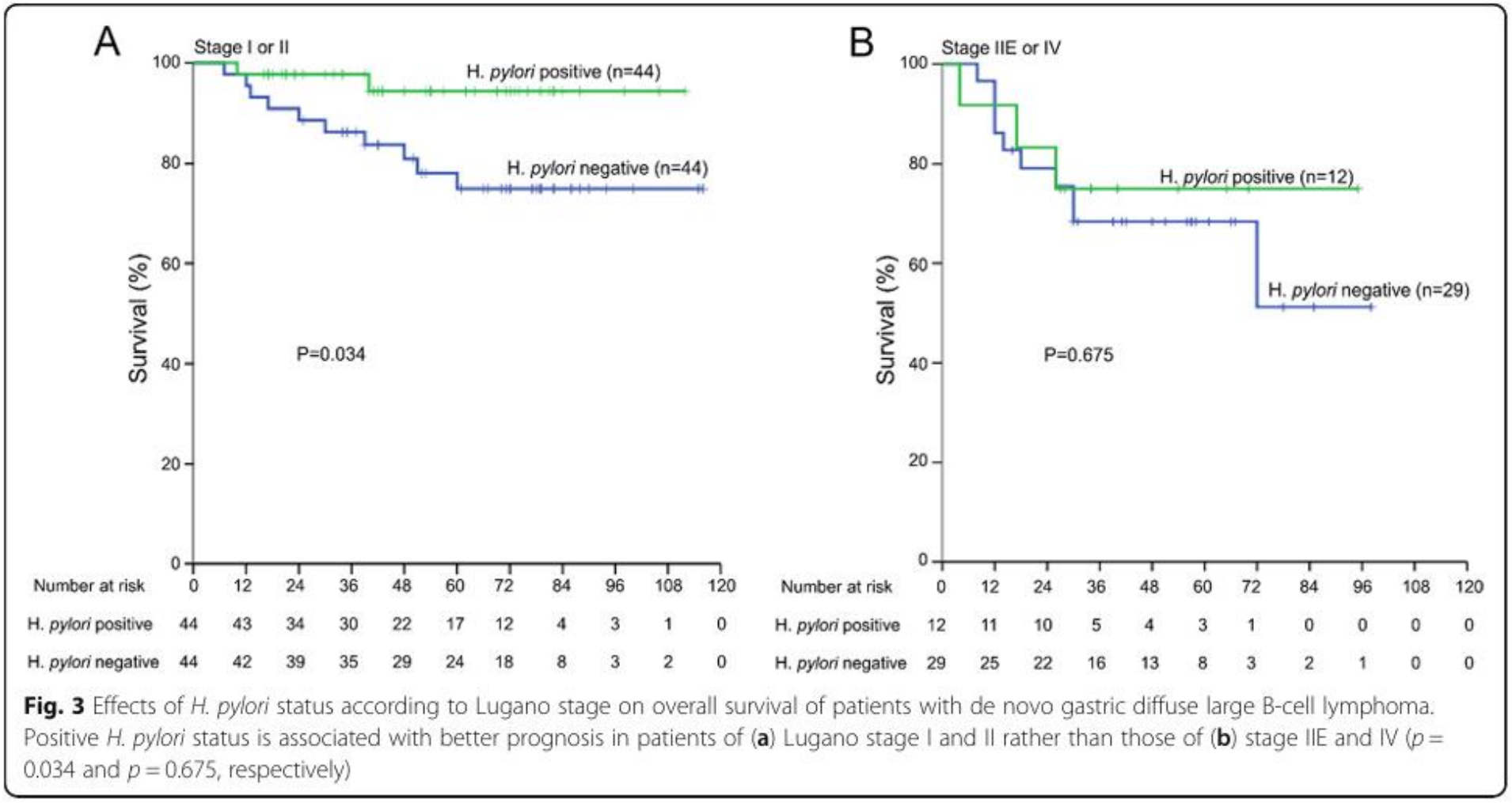


Fig. 3 Effects of *H. pylori* status according to Lugano stage on overall survival of patients with de novo gastric diffuse large B-cell lymphoma. Positive *H. pylori* status is associated with better prognosis in patients of (**a**) Lugano stage I and II rather than those of (**b**) stage IIE and IV ($p = 0.034$ and $p = 0.675$, respectively)

S-H kuo et al Blood Cancer Journal 2014

DLBCL AND HELICOBACTER PILORI

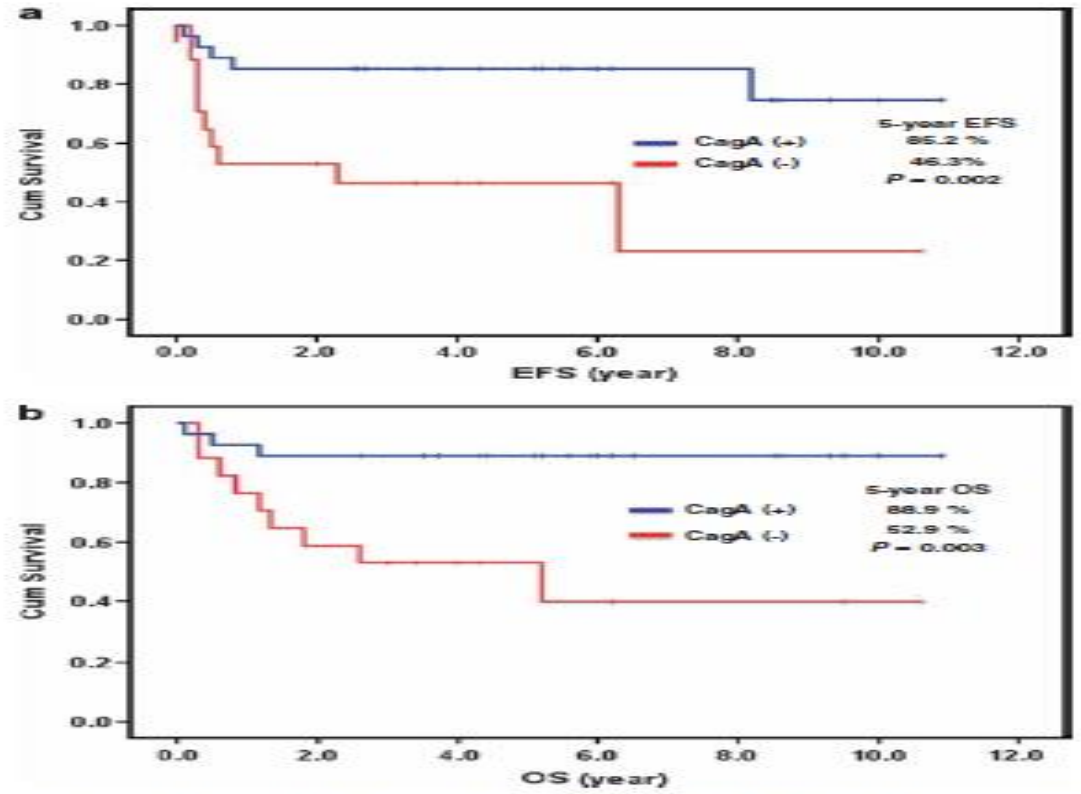


Figure 3. Association of CagA expression with clinical outcome in HP-positive gastric 'pure' DLBCL. (**a**) Relationship of CagA status to EFS. (**b**) Relationship of CagA status to OS.

S-H kuo et al Blood Cancer Journal 2014

DLBCL AND HELICOBACTER PILORI

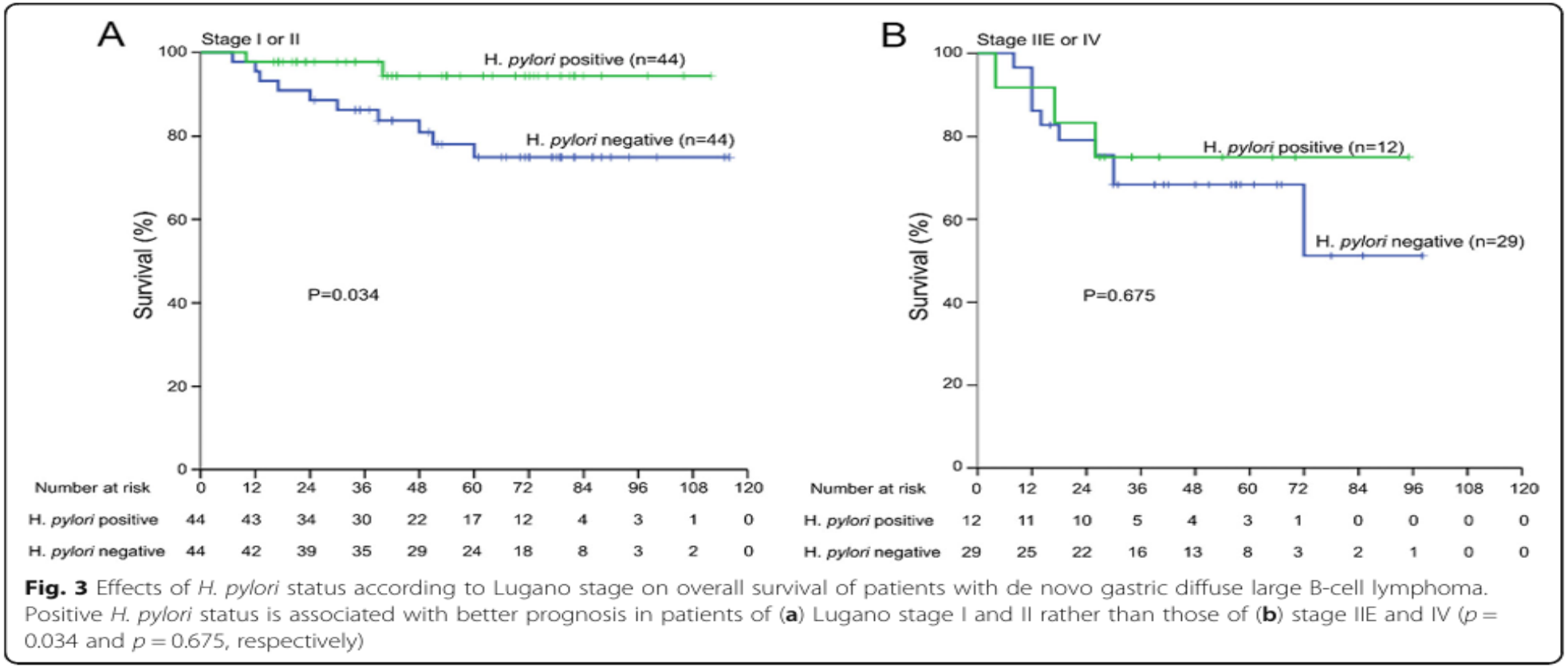


Fig. 3 Effects of *H. pylori* status according to Lugano stage on overall survival of patients with de novo gastric diffuse large B-cell lymphoma. Positive *H. pylori* status is associated with better prognosis in patients of (**a**) Lugano stage I and II rather than those of (**b**) stage IIE and IV ($p = 0.034$ and $p = 0.675$, respectively)

Yuang Chen et al. BMC Cancer 2019

Pathology

DLBCL is described by diffuse proliferation of large, atypical cells, with vesicular nuclei, prominent nucleoli, and basophilic cytoplasm.

These cells typically express CD19, CD20, CD22 and CD79a (pan-B-cell markers).

Bcl-6 is expressed in 60% of cases.

FISH can identify poor prognostic subtypes of DLBCL, such as double-hit (DH) or triple-hit (TH) lymphomas (high-grade, B-cells), characterized by translocations of MYC and Bcl-2 and/or Bcl-6

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

Pathology

Gene expression profiling distinguishes DLBCL into GCB and non-GCB or activated B-cell-like (ABC) subtypes based on the cell of origin profile.

ABC lymphomas show a worse prognosis than GCB lymphomas.

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

DLBCL gástrico

MALT gástrico

DHT/THT DLBCL gástrico

DLBCL gástrico

HP+ DLBCL de novo

HP- DLBCL

DLBCL transformado

CD20 negative DLBCL HP+

Formas localizadas
Centrogerminal
Quimiosensibilidad
Pronóstico favorable

Pronóstico desfavorable
Algunos EBV+ de mal pronóstico

Pronóstico similar a HP+ DLBCL

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

CLINICAL MANIFESTATIONS

The stomach is the most common site for the development of extranodal lymphomas in the GI tract, accounting for 60% of cases, followed by the small bowel, ileum, cecum, colon and rectum.

Distinguishing PGL from secondary dissemination of the stomach due to primary nodal lymphoma can be difficult.

No peripheral and mediastinal lymphadenopathy at the time of diagnosis, no spleen or liver infiltration and normal blood counts are in contrast to the presence of a secondary gastric lymphoma.

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

CLINICAL MANIFESTATIONS

In recent years, a more specific Lugano staging system for PGLs was proposed and applied based on the Lugano score, which includes the following stages:

Stage IE — Lymphoma is confined to the GIT (single lesion or multiple noncontiguous lesions):
IE1 = mucosa, submucosa;
IE2 = muscularis propria, serosa;
Stage II — Lymphoma extends into the abdomen from the primary site within the GI tract:
II1 = local nodal involvement;
II2 = distant nodal involvement; Stage IIE — Penetration of serosa to involve adjacent organs or tissues;
Stage IV — Disseminated extranodal involvement or concomitant supra diaphragmatic nodal involvement.
Note: Stage III does not exist because gastric lymphoma is always below the diaphragm

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

CLINICAL MANIFESTATIONS

Some patients with DLBCL PGL also have a MALT component.

The 5-year PFS and OS estimates were similar when de novo DLBCL patients were compared with DLBCL/MALT patients, suggesting that patients with a MALT component, along with DLBCL, might have the same biological type of lymphoma as de novo DLBCL patients

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

Estudio Peruano DLBCL gástrico

Tabla 1. Características clínicas en los pacientes con LCGBD 1° gástrico EC I – II del HNERM diagnosticados 2010-2013 según las variables rutinarias.

	n	%
Pacientes	26	-
Edad		
Mediana (rango)	62 (30, 84)	
>60	16	61.5
Sexo Masculino	17	65.4
Escala ECOG		
0	5	19.2
1	21	80.8
Estadio clínico		
I	17	65.4
II	9	34.6
Síntomas B (+)	14	53.8

Tabla 4. Modalidades de tratamiento recibido y respuesta obtenida en los pacientes con LCGBD 1° gástrico EC I – II del HNERM diagnosticados 2010-2013.

	n	%
Cirugía		
No	22	84.6
Si	4	15.4
Esquema		
R-CHOP x ≤ 3 cursos	4	15.3
R- CHOP x 4 cursos	2	7.7
R- CHOP x 5-6 cursos	10	38.4
CHOP x 6 + RT Consolid	1	3.8
R-CHOP X 4 + RT Consolid	5	19.2
R-CHOP X 6 + RT Consolid	4	15.3
Respuesta clínica		
RC	21	84.0
RP	-	
EE	1	4.0
PE	3	12.0
Desc	1	-

S. Paredes et al. Data unpublishied

Estudio Peruano DLBCL gástrico

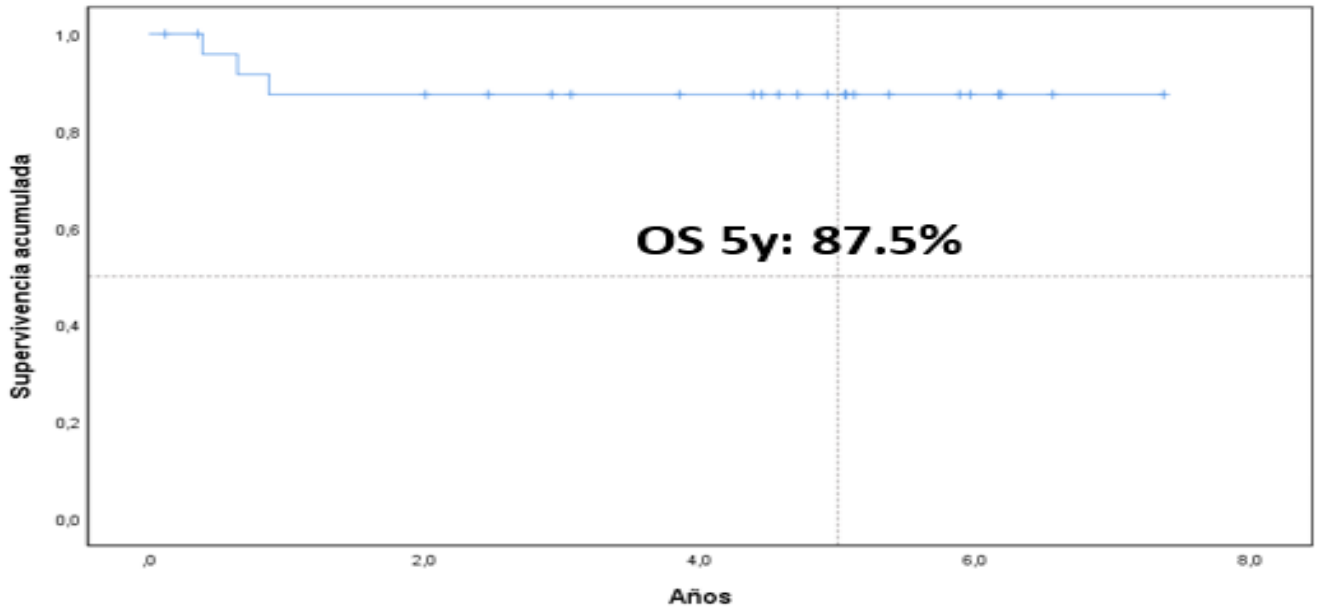


Figura 1. Supervivencia global de los pacientes con LNH DCGB 1° Gástrico EC I-II del HNERM diagnosticados 2010-2013.

S. Paredes et al. Data unpublishied

PROGNOSTIC FACTORS

Helicobacter pylori negativity

Lugano stage II2/IIE/IV

Elevated serum LDH level

Epstein-Barr virus infection

Deficiency of gene translocation involving the immunoglobulin heavy chain [

Z. Bai et al .Turk J Hematol 2020

Treatment

Traditionally, the R-CHOPx 4 + RT regimen has demonstrated significant results.

However, a recent SEER study does not demonstrate a benefit of radiotherapy on overall survival.

Recent management guidelines suggest that a R-CHOPx 6 cycles regimen may be the new standard.

We do not yet have a study comparing immunochemotherapy strategies based on the new classification of gastric DLBCL according to HP status.

Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

Abstract Title : Real-world outcomes of primary gastric diffuse large B cell lymphoma in Latin America: A multicenter cohort from the grupo de estudio latinoamericano de linfoproliferativos (GELL)

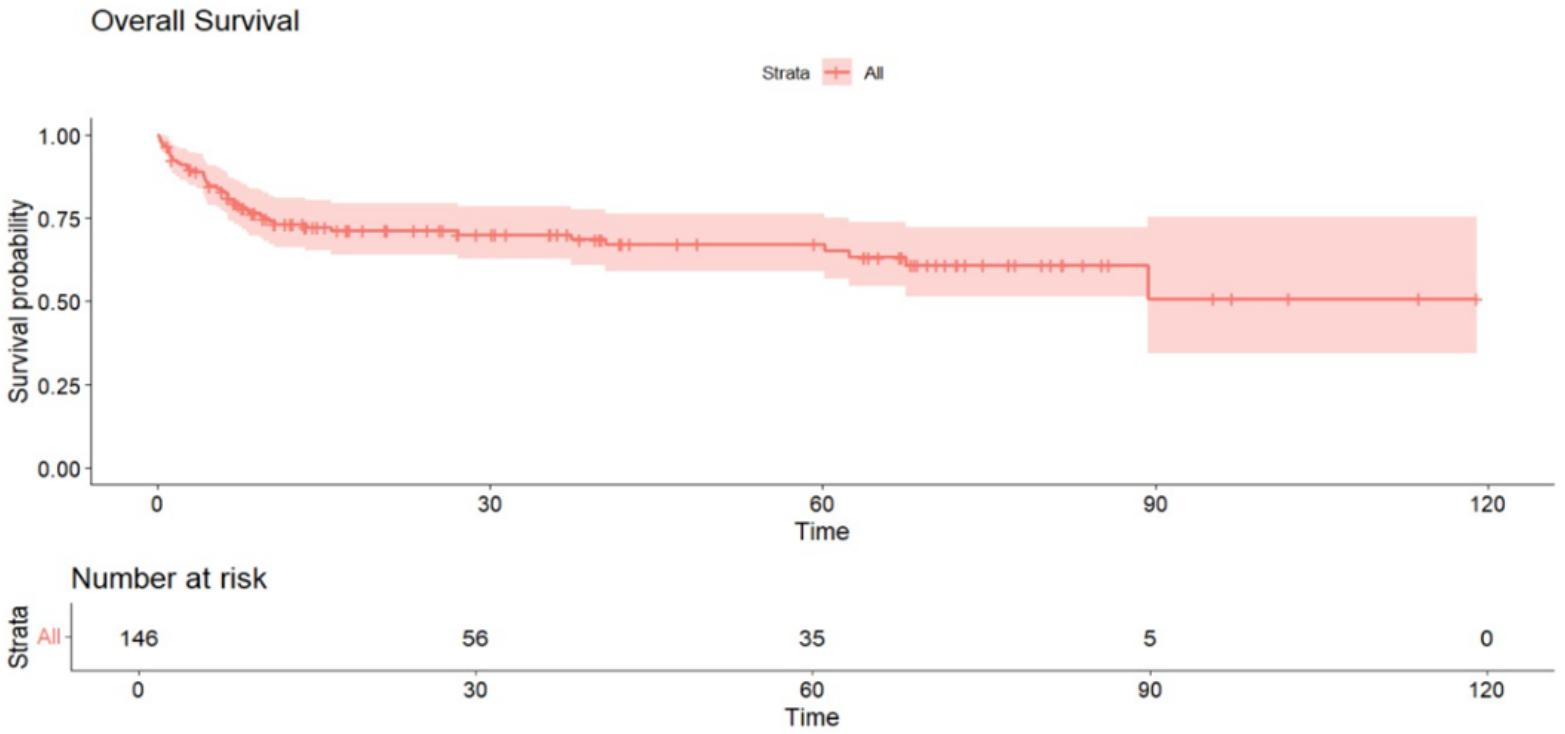
A total of 157 patients were included.
The median follow-up time was 35.5 months (IQR : 13.1–68.6) and 50 (32%) died during follow-up.

Compared to survivors, deceased patients were older (mean 68 vs. 61 years), had worse ECOG performance status (≥2: 20% vs. 1.9%), more B symptoms (62% vs. 41%), and advanced clinical stage III–IV (63% vs. 36%) .

Hemoglobin <10 g/dL was more frequent among the deceased (44% vs. 25%), as were hypoalbuminemia and elevated LDH .

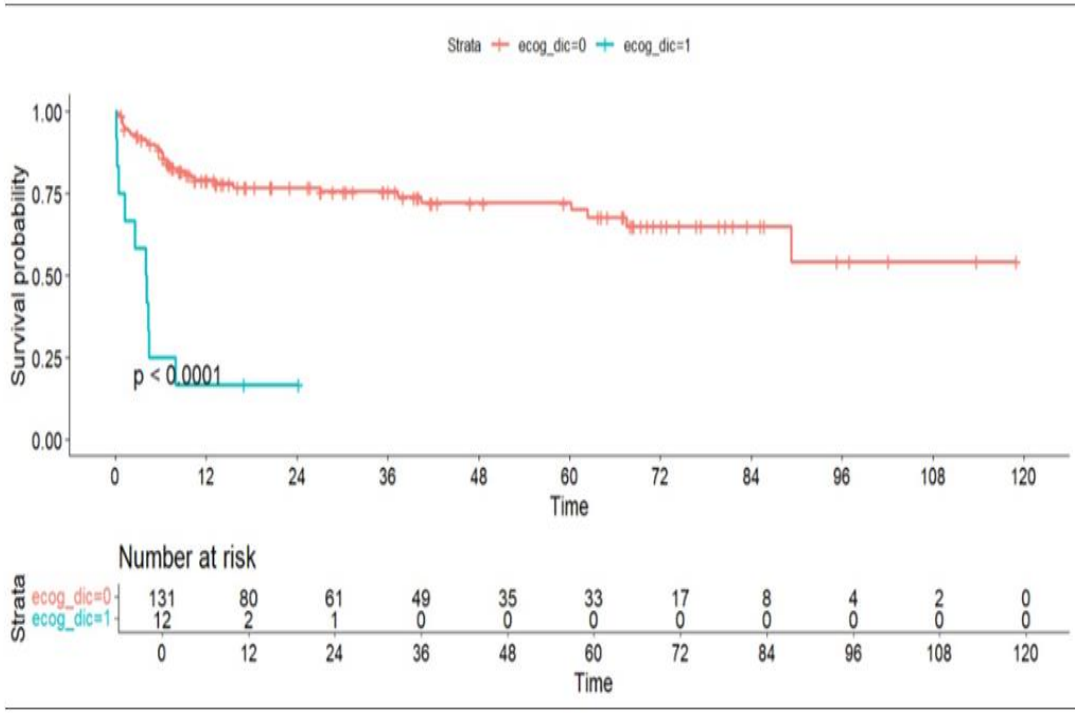
Refractory or relapsed disease occurred in 30% of deceased patients versus 5% of survivors . Most patients received R-CHOP or equivalent first-line therapy .

Abstract Title : Real-world outcomes of primary gastric diffuse large B cell lymphoma in Latin America: A multicenter cohort from the grupo de estudio latinoamericano de linfoproliferativos (GELL)



Abstract Title : Real-world outcomes of primary gastric diffuse large B cell lymphoma in Latin America: A multicenter cohort from the grupo de estudio latinoamericano de linfoproliferativos (GELL)

In multivariable analysis,
Age (HR: 1.05 per year; 95% CI: 1.02–1.07; p < 0.001).
ECOG ≥2 (HR: 7.32; 95% CI: 3.09–17.3; p < 0.001).
Advanced stage (HR: 2.57; 95% CI: 1.27–5.17; p = 0.008)
were independently associated with increased mortality

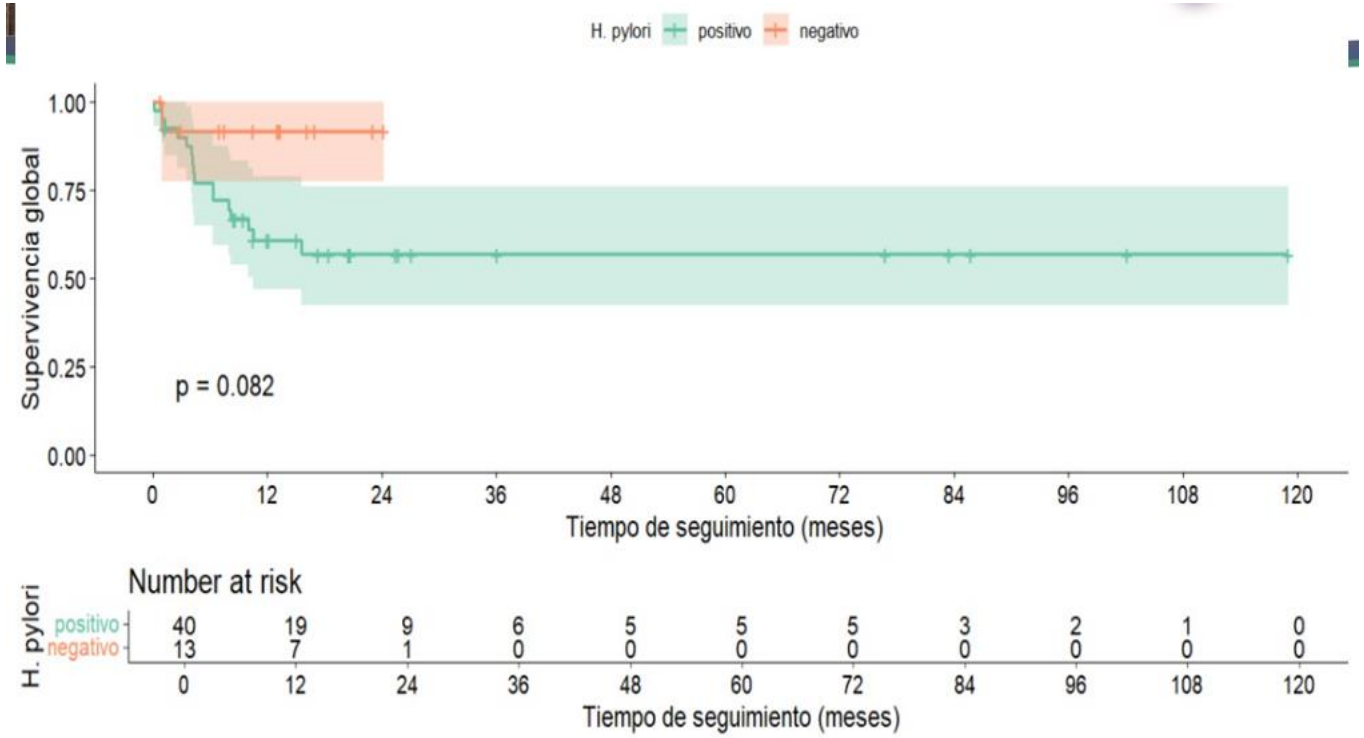


HP+ vs. HP (-)

In a subanalysis of 60 patients with known HP status:

HP-positive patients had higher OS at 12 and 24 months (91.7% vs. 60.7% and 56.7%, respectively) and higher complete response rates (61% vs. 33%).

Disease progression, relapse, and treatment-related mortality were more frequent among HP-negative patients



Supervivencia global según radioterapia

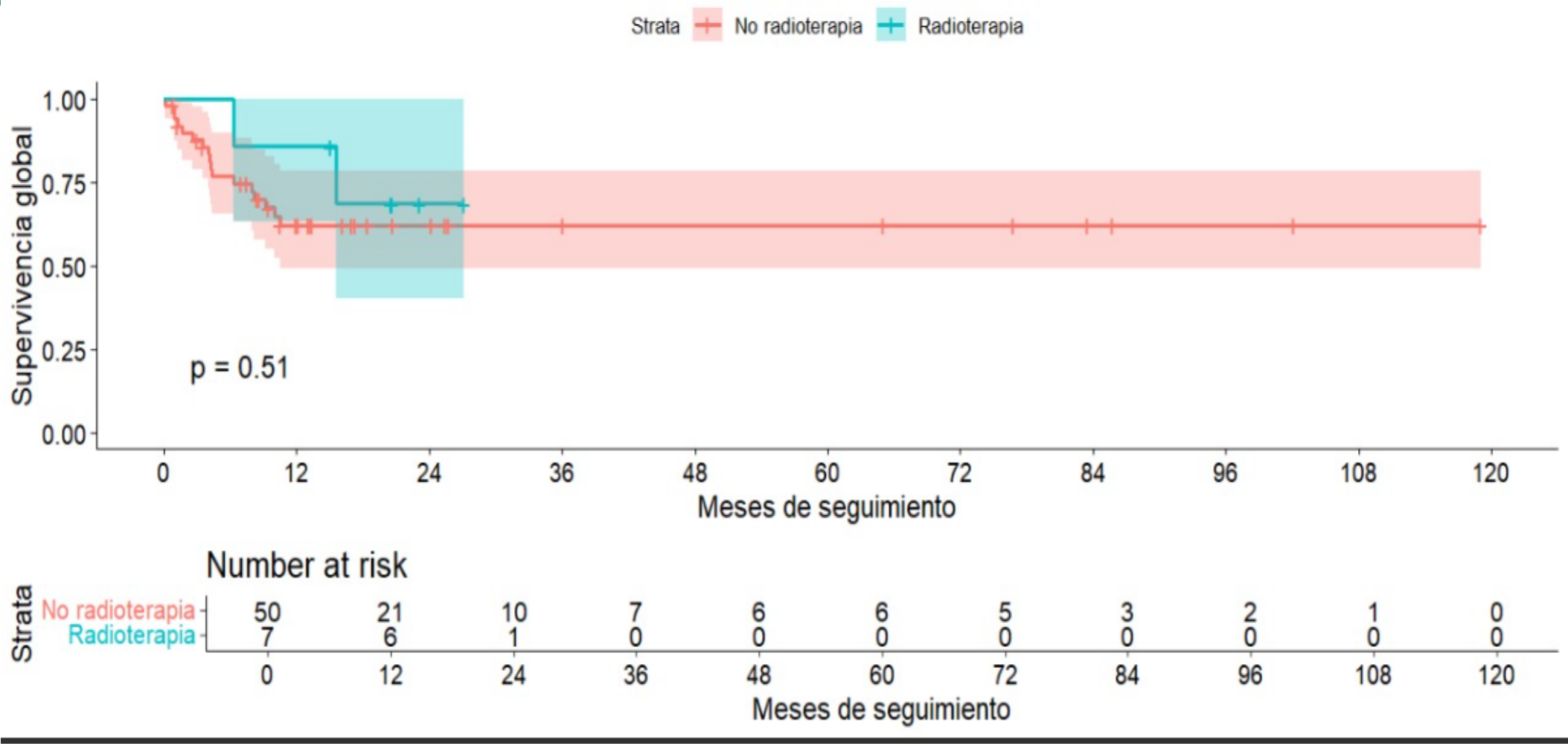


Table 1 Studies comparing rituximab-cyclophosphamide doxorubicin vincristine prednisone *vs* cyclophosphamide doxorubicin vincristine prednisone for diffuse large B-cell lymphoma primary gastric lymphomas

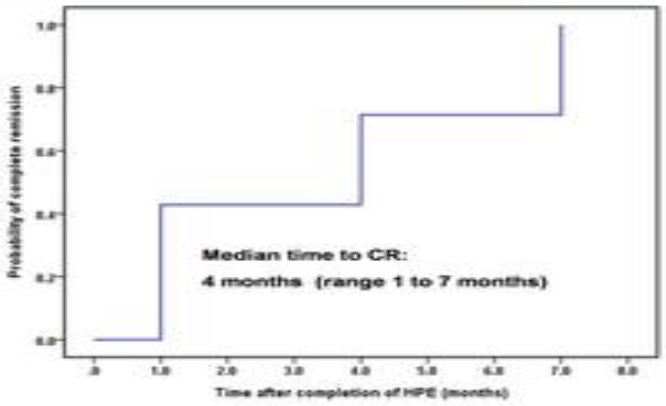
Ref.		Number of Pts	R-CHOP OS	CHOP OS	R-CHOP PFS	CHOP PFS	Comments
Sohn *et al* [19], 2012	Double-arm Retrospective Study (R-CHOP *vs* CHOP as 1st line treatment)	93 (55 R-CHOP, 38 CHOP)	3-yr 84.7% ($P > 0.05$)	3-yr 94.7% ($P > 0.05$)	3-yr 81.7% (EFS) ($P > 0.05$)	3-yr 86% (EFS) ($P > 0.05$)	CR: (CHOP: 93.9%), (R-CHOP: 92.5%)
Liu *et al* [62], 2018	Double-arm Retrospective Study (diagnosis: 1973-2000 era *vs* 2001-2014 era of immuno-CT)	SEER Database 7051 [(4186, 1973-2000), (2865, 2001-2014)	5-yr 53% ($P = 0.001$)	5-yr 47% ($P = 0.001$)			
Tanaka *et al*[20], 2012	Single-arm Retrospective Study (R-CHOP)	95	3-yr 91% (localized disease); 3-yr 95% (localized disease); 3-yr 64% (localized disease)		3-yr 91% (localized disease); 3-yr 92% (localized disease); 3-yr 43% (localized disease)		6c. R-CHOP; 3-4 c. R-CHOP plus radiotherapy; R-CHOP ± radiotherapy
Couto *et al*[17], 2021	Single-arm Retrospective Study (R-CHOP)	101	Not reached		Not reached		80% CR (after 1st line); 54% CR (3 yrs FU)

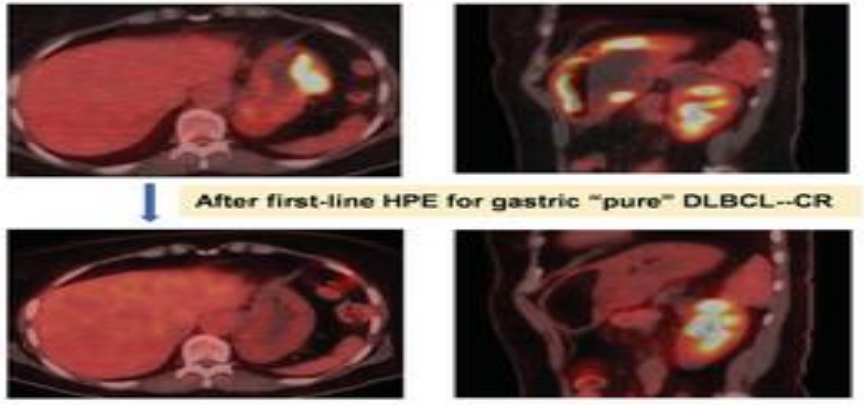
Diamantidis MD, Papaioannou M, Hatjiharissi E. Primary gastric non-Hodgkin lymphomas: Recent advances regarding disease pathogenesis and treatment. World J Gastroenterol. 2021

Can we treat with antibiotictherapy HP+ gastric DLBCL =

First-line *Helicobacter pylori* eradication therapy (HPE)
: two weeks of antibiotics treatment

Complete remission (CR) (n = 7)	Partial remission (PR) (n = 3)	Stable disease/Progressive disease (n = 8)
Close follow-up Endoscopic examination CT scan	Rituximab, cyclophosphamide, vincristine and prednisolone (R-COP, n = 2) R-P (n = 1)	R-COP (n = 7) R-COP plus doxorubicin (n = 1)
All: no recurrence Duration of CR: median 62.1 months (95% CI: 31.3–74.3 months)	CR after rituximab-based regimen (n = 3) No recurrence	CR after rituximab-based regimen (n = 8) 1 died of pneumonia The other: lymphoma-free





After first-line HPE for gastric "pure" DLBCL--CR

TREATMENT

TWO FACTORS CAN BE PREDICTIVE BIOMARKERS TO ANTIBIOTICTHERAPY:

1.- BCL10

2.- Increased NF KB

Complications

Surgery as a first option:

- Perforation
- Piloric sydrome
  Distal lesions with suboclusive obstructions
- Massive bleeding

Shen Y, et al. Influence of severe gastrointestinal complications in primary gastrointestinal diffuse large B-cell lymphoma. *Cancer Manag Res*. 2021

Complications

Bleeding:

Gastric bleeding is a frequent complication, with some studies reporting a 2-3.5% incidence and others up to 7-19%. The risk of bleeding may increase after chemotherapy, especially if there was a history of bleeding before treatment.

Management:

- Conservatory
- Embolization
- Control endoscopic
- Surgery
- Radiotherapy ?

Shen Y, et al. Influence of severe gastrointestinal complications in primary gastrointestinal diffuse large B-cell lymphoma. *Cancer Manag Res*. 2021

Complications

Stenosis

Primary

Surgery

- Gastrectomy
- Derivation gastrojejunal --- laparoscopic

Secondary

After 2 months of the begininig of chemotherapy

Fibrosis

Derivation gastrojejunal

Shen Y, et al. Influence of severe gastrointestinal complications in primary gastrointestinal diffuse large B-cell lymphoma. *Cancer Manag Res*. 2021

Complications

Perforation:

Gastric perforation is an uncommon but serious complication with a reported incidence of 1-2% and a high mortality rate.

Fistula:

Gastrosplenic fistula, a rare complication, can occur after chemotherapy in patients with contiguous gastric and splenic involvement.

Shen Y, et al. Influence of severe gastrointestinal complications in primary gastrointestinal diffuse large B-cell lymphoma. *Cancer Manag Res*. 2021

Conclusions

HP+ gastric DLBCL is a distinct entity from HP (-) with greater sensitivity to immunochemotherapy and better survival.

Peru has a high incidence of HP+ gastric DLBCL because it is an endemic country for CAG-A HP.

All patients with primary gastric DLBCL should have their HP status assessed to determine their prognosis.

HP is a protective factor in gastric DLBCL, similar to what EBV is for gastric cancer.

Complications are frecuent.

Conclusions

All patient with G-DLBCL should have breath test.

G-DLBCL HP+ should begin RCHOP + antibiotic therapy .

We should avoid radiotherapy as consolidation because it could increase the risk of Gastric cancer (in the HP context) and can produce stenosis.

We should not use radiotherapy for control of bleeding.

Surgery should be the first option in : perforation, massive bleeding or obstruction.

HP+ G-DLBCL could receive only 4 cycles of R-CHOP?

HP+G-DLBCLcould be treatetd with ATB?

.

T