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RISK FACTORS FOR PROGRESSION TO GASTRIC NEOPLASTIC LESIONS IN PATIENTS WITH ATROPHIC GASTRITIS.

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**RISK FACTORS FOR PROGRESSION TO GASTRIC
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GASTRITIS.**

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3 **RISK FACTORS FOR PROGRESSION TO GASTRIC NEOPLASTIC LESIONS IN**
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5 **PATIENTS WITH ATROPHIC GASTRITIS.**
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25 **Running Head** : Risk for neoplasia in atrophic gastritis
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29 **Key Words:**Atrophic Gastritis (AG), Gastric Cancer (GC), Gastric Neoplastic Lesions (GNL),
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31 Noninvasive Neoplasia (NiN).
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ABSTRACT

Background: Atrophic gastritis (AG), involving the gastric body mucosa, predisposes to gastric neoplastic lesions (GNL). In AG patients, regular gastroscopic-histological follow-up for GNL is not recommended.

Aims: To evaluate in a cohort of AG patients risk factors for the progression to GNL.

Methods: 300 AG patients (205 females, age 54[18-78]years) underwent gastroscopy with six gastric antrum and body biopsies. All patients had at least one follow-up gastroscopy/histology at an interval of at least one year after the AG diagnosis. Baseline clinical and histological features were analyzed as risk factors for the development of GNL by Cox-regression.

Results: During a median follow-up of 4.3 (1-16.5)years, 15 GNL were detected in 14 of the 300 AG patients: 3 were gastric cancer, whereas 12 were non-invasive neoplasia. The annual incidence for GNL was 1%. Cox-regression analysis identified the following risk factors: age over 50 years (HR 8.8, 95%CI 1.2-68.4), atrophic pangastritis (HR 4.5, 95%CI 1.5-14.1) and severe intestinal metaplasia in the gastric body (HR 4.0, 95%CI 1.3-11.8).

Conclusion: Atrophic pangastritis, severe body intestinal metaplasia and/or age over 50 years increase the risk for developing GNL in AG patients. In this subset of patients, an endoscopic-histological follow-up for GNL surveillance may be worthwhile.

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer worldwide and the second cause of cancer-related death (1-2). Nowadays, it is accepted that the carcinogenesis involves a multistep progression from *H pylori*-related chronic inflammation of the gastric mucosa, to atrophic gastritis (AG), intestinal metaplasia, dysplasia and, finally, intestinal-type GC (3). Other authors have proposed the concept of 'gastritis of the carcinoma phenotype' showing that the corpus-predominant gastritis is "per se" a condition at increased risk for the development of GC (4-6). When the gastritis involves the gastric body, pathophysiological changes, such as increased pH, reduced ascorbic acid and scavenging of nitrites and other potential carcinogenic substances, potentially lead to the development of gastric neoplastic lesions (GNL) (7-8).

AG, involving the gastric body mucosa, is considered a precursor condition for GC and noninvasive neoplasia (NiN) (3, 9). Previous studies reported a varying progression rate of AG to GC up to 2% per year, while data on progression of AG to NiN are scarce (10-12). However, these studies were mostly performed on small series of patients and based on older histological classifications.

In patients with AG, regular gastroscopic follow-up for GC surveillance is not considered cost-effective in Western countries and not recommended (13). As suggested in a recent review, to evaluate the exact value of surveillance in patients with AG and establish follow-up frequencies, more precise data, preferably obtained in large prospective studies with adequate follow-up, are needed (14). Thus, the aim of the present study was to evaluate in a prospective cohort of AG patients risk factors for the progression to gastric neoplastic lesions.

METHODS

Patients and Study Design

Between January 1992 and June 2008, as the result of a screening programme for atrophic body gastritis, we diagnosed this condition in 403 consecutive patients (269 females, median age 55

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3 years, range 18-95 years) (11,15). At diagnosis of AG, all patients underwent a clinical interview
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5 based on a structured questionnaire to assess personal and clinical data, family history for GC
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7 and smoking habit. All patients were informed about the increased risk of GC associated with
8
9 AG and about the need to undergo regular follow-up by gastroscopy.
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12 Inclusion criteria were the presence of AG and at least one follow-up investigation by
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14 gastroscopy with biopsies at an interval of at least one year after the diagnosis of AG. As shown
15
16 in **Figure 1**, 103 (25.6%) patients of the baseline population dropped-out during follow-up and
17
18 the final follow-up population comprised 300 patients (205 females, median age 54 years, range
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20 18-78 years).
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24 **Diagnosis of Atrophic Gastritis and Gastric Neoplastic Lesions**

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26 The diagnosis of AG was based on the histological confirmation of gastric body atrophy and the
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28 presence of fasting gastrin above upper normal values (15). All patients underwent gastroscopy
29
30 with three biopsies taken from the gastric antrum (within 3 cm of the pyloric ring, lesser and
31
32 greater curve, anterior or posterior wall) and three biopsies from the midbody along the greater
33
34 curve (16). In case of lesion, additional biopsies were obtained. The degree of gastritis was
35
36 assessed according to the updated Sydney System (17). Atrophy of the gastric body mucosa was
37
38 defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal
39
40 glands. Atrophy of the antral mucosa was defined as focal or complete disappearance of antral
41
42 glands or their replacement by intestinal metaplastic epithelium (15). The definitions of GNL
43
44 (NiN and GC) were based on the Padova International Classification and WHO guidelines (18-
45
46 19). All biopsies were examined independently by two experienced pathologists (CB, MM),
47
48 unaware of the clinical data of the patients. In the event of disagreement, the biopsies were re-
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50 examined simultaneously by both pathologists until agreement was reached (15).
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57 In all patients, fasting gastrin levels and Pepsinogen I were measured. Gastrin levels were
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59 evaluated by a specific radioimmunoassay (RIA: normal values ≤ 40 pg/ml); Pepsinogen I was
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measured using a commercial RIA kit (Pepsik; Sorin, Saluggia, Italy; normal values 20-80

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3 ng/ml) (15). The presence of anaemia was evaluated in all AG patients: pernicious anaemia was
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5 defined as low hemoglobin concentration, MCV>100 fl together with low cobalamin levels and
6
7 iron deficiency anaemia was defined as low hemoglobin concentration, MCV<80 fl and
8
9 ferritin<30 ng/ml (20-21).
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12 **Assessment of *H pylori* Status and Eradication**

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15 *H pylori* infection was considered positive when the bacterium (Giemsa stain) and/or the
16
17 presence of neutrophil granulocytes were detected at histology and/or on the basis of a positive
18
19 IgG titre for *H pylori* (11). *H pylori* IgG antibodies were determined using ELISA commercial
20
21 kit (GAP test IgG, Biorad, Milan, Italy). *H pylori* positive AG patients received triple therapy
22
23 (bismuth-based triple regimens). The absence of *H pylori* and neutrophil granulocytes at
24
25 histology and a decrease by at least 50% in the initial titre of *H pylori* IgG was considered as a
26
27 criterion for the successful cure of infection (16). Overall, 192 (64%) of patients were treated
28
29 and successful cure of infection was achieved in 62.5%.
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33 **Follow-up Protocol**

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36 In general, the first follow-up gastroscopy was scheduled at intervals between 2 and 4 years after
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38 diagnosis of AG, during which the same baseline bioptic sampling was repeated (22).
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41 In the case of *H pylori* eradication treatment, a gastroscopy/histology was performed at 6 months
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43 to evaluate the efficacy of cure, and then patients were monitored by the general follow-up
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45 protocol.
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48 If NiN was detected, an extensive bioptic sampling of at least ten biopsies of the gastric mucosa
49
50 was taken after 6 and 12 months for low-grade NiN and after 3, 6, and 12 months for high-grade
51
52 NiN (23). If NiN was not confirmed at two following gastroscopies, patients were followed by
53
54 the general follow-up protocol.
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57 When gastric polyps were detected, polypectomy was performed. In the case of a histological
58
59 diagnosis of GC the indication for mucosectomy and/or surgery was evaluated.
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3 At any time, when patients referred the onset of alarm symptoms, such as dysphagia, vomiting,
4
5 dyspepsia, and/or recent onset or worsening of iron deficiency anaemia, gastroscopy was
6
7 performed immediately.
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10 **Data Analysis and Statistical Evaluation**

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12 The occurrence of GNL in the baseline population and in the follow-up population of AG
13
14 patients was evaluated, and data were expressed as prevalence and incidence rate (person-year).
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16 Standard descriptive statistics were expressed as median and range or, when appropriate,
17
18 absolute counts and percentages. Intervals between initial AG diagnosis and GNL diagnosis
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20 were analyzed by Kaplan-Meier analysis. Sydney system scores from AG patients who
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22 developed GNL during follow-up and those who did not were analyzed using Fisher's exact test.
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Histological data were analyzed also according to OLGA System (24), which describes the
extension of atrophy with or without metaplasia in both antral and body gastric mucosa. The
scores of atrophy from antral and body gastric mucosa are combined using a scale ranging from
0 (absence of atrophy and metaplasia) to IV (atrophy involving antrum and gastric body).
Univariate and multivariate Cox-regression analysis was performed to identify risk factors for
progression to GNL. The incident GNL were coded with value 1 in the binary dependent
variable. The following characteristics were considered as covariates: age over 50 years, gender,
presence of atrophic pangastritis defined as the concomitant presence of atrophy in the gastric
antrum and body, presence of severe intestinal metaplasia in the gastric body, presence of
intestinal metaplasia in the gastric antrum, presence of stage IV of OLGA system, presence of
pernicious anaemia, presence of *H pylori*. For each covariate, the hazard ratio (HR) and 95% CI
are reported. Cox-regression analysis was run using MedCalc version 10.1.2, Mariakerke,
Belgium. A p value of less than 0.05 was considered statistically significant.

58 **RESULTS**

59 **Baseline**

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3 At the time of diagnosis of AG, ten GNL (2.5 %) were detected in ten of the 403 AG patients (6
4 female, median age 62 [range 49-77] years. In one patient (0.2%) a GC was diagnosed and the
5 remaining nine patients had a diagnosis of NiN (2.3%), which was low-grade in all but one. In
6 detail, the patient (male, 63 years of age) with intestinal-type adenocarcinoma (T2N0M0) had
7 presented with iron deficiency anaemia and an ulcerative lesion in the gastric body in the context
8 of a OLGA stage 3 AG with severe intestinal metaplasia. The patient underwent gastrectomy
9 and is to date alive. As far as regards NiN, eight patients had a low-grade NiN: in six of them the
10 NiN were detected in apparently normal mucosa in the gastric antrum and in two patients
11 adenomas with low-grade dysplasia (<1 cm) were found in the gastric body. One patient had an
12 adenoma with high-grade dysplasia (3 cm) located in the gastric antrum.
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27 Follow-up

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29 During an overall median follow-up of 4.3 years (range 1-16.5 years), 15 (5.0%) GNL were
30 detected in 14 of the 300 AG patients (7 female, median age 57 [range 51-77 years]): three GNL
31 were GC, whereas the remaining 12 GNL were NiN. Thus, an annual incidence rate (person-
32 year) of 1% for all GNL and of 0.2% for GC was observed. **Figure 2** shows the Kaplan-Meier
33 curves indicating the intervals between initial AG diagnosis and GNL diagnosis.
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41 **As shown in the Table 1**, all three GC were intestinal-type adenocarcinomas located in the
42 gastric antrum and were diagnosed 8, 5 and 1 years after diagnosis of AG in one male (aged 51
43 years) and two female patients (aged 51 and 77 years), respectively. The male patient had a
44 negative follow-up gastroscopy two years before diagnosis of GC and had had no evidence of
45 GNL during previous follow-up, whereas the two female patients had a previous diagnosis of
46 low-grade NiN one year before diagnosis of GC. The stage of the GC was T2N1M0 in the male
47 patient, and T1N0M0 in the two female patients. In the first case, follow-up gastroscopy was
48 performed due to the new onset of iron deficiency anaemia and dyspepsia; in the other two cases
49 the diagnosis of GC was yielded at 12 months after the diagnosis of low-grade NiN (one present
50 at the time of diagnosis of AG and the other diagnosed at 4-year-follow-up). After gastrectomy,
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3 the male patient underwent chemotherapy and died for neoplastic disease progression, one
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5 female patient died for complications after surgery and one female patient is alive and to date
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7 free of neoplasia.
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10 Of the 12 NiN, eight were located in the gastric antrum and four in the body, all but one were
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12 low-grade, four were polyps and eight were detected in apparently normal mucosa. Seven low-
13
14 grade NiN on apparently normal gastric mucosa were confirmed at following controls, and at the
15
16 longest follow-up available all patients are alive and free of neoplasia. After polypectomy, one
17
18 low-grade and one high-grade NiN recurred in two patients; at the longest follow-up available
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20 also these patients are alive and free of neoplasia.
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24 **Risk Factors**

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26 **Figure 3** shows the comparison of baseline atrophy and intestinal metaplasia scores according to
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28 Sydney System between AG patients who developed GNL during follow-up (n=14) and those
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30 who did not (n=286). AG patients with GNL had more frequently severe intestinal metaplasia in
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32 the gastric body (Figure 3b; p=0.001), and the concomitant presence of antral atrophy and
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34 intestinal metaplasia (Figure 3c,3d; p<0.001). Moreover, AG patients who developed GNL at
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36 follow-up had more frequently OLGA stage IV compared to AG patients who did not (15% vs.
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38 3%, p=0.02). The baseline values of gastrin and pepsinogen I were not different between AG
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40 patients who developed GNL and who did not (gastrin 500[40-2500] pg/ml vs 500[40-2700]
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42 pg/ml respectively; pepsinogen I 10[5-41] ng/ml vs 10[3-70] ng/ml respectively). No difference
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44 was found between two groups with regard to smoking habit and family history for GC (data not
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46 shown).
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52 As shown in the **Table 2**, Cox-regression analysis identified the following significant risk factors
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54 for the development of GNL: age over 50 years (HR 8.8), the presence of atrophic pangastritis
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56 (HR 4.5) and the presence of severe intestinal metaplasia in the gastric body (HR 4.0). Other
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58 features such as the gender, Stage 4 of OLGA system, the presence of pernicious anaemia as
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60 well as the positivity to *H pylori* were not predictive for the development of GNL. Among

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3 patients with pernicious anaemia (n=129), 53 (41%) were *H pylori* positive, among those
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5 without pernicious anaemia (n=171), 139 (81.3%) were *H pylori* positive.
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10 DISCUSSION

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12 This study found three independent risk factors for the development of GNL in AG
13 patients: age over 50 years, the presence of atrophic pangastritis and of body severe intestinal
14 metaplasia. A previous study reported that patients aged >45 years had an about twofold
15 increased risk of intestinal metaplasia progression than younger subjects (25). In a recent large
16 cohort study, it was shown that the increasing age at initial diagnosis was associated with the
17 progression to more advanced lesions and to GC (26). These findings suggest that age could be
18 considered as a criterion to select a subgroup of AG patients for GNL surveillance as
19 recommended for other GI tumors such as colorectal neoplasia screening.
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22 We found that the presence of atrophic pangastritis increased the risk to GNL progression by 4.5
23 times. This finding confirms the result of previous works (11,27-28). In particular, in our 2005
24 study, we found that the presence of atrophic pangastritis was strongly associated with the
25 presence of GNL (11). In the present study, this finding is even strengthened by an increased
26 sample size of the AG cohort, a longer follow-up period and a more accurate statistical
27 evaluation. On the contrary, this finding may be in contrast with older papers, in which corpus-
28 restricted atrophy associated with pernicious anaemia, was considered at higher risk for GC (29-
29 30). However, the comparison with older studies may be difficult for methodological differences
30 and because the extension of atrophy in the stomach has not been systematically evaluated in
31 previous literature.
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34 Finally, this study confirms the presence of severe intestinal metaplasia in the gastric body as a
35 risk factor (HR 4) for progression to GNL. In the literature, the intestinal metaplasia extension
36 was already related to a higher risk of GC (28). Indeed, an extensive replacement of normal
37 gastric mucosa with intestinal metaplasia is often considered as a hallmark of severity of AG.
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3 This study observed an incidence rate person-year of 0.2% for GC and of 1% for all GNL. The
4 reported rate of annual incidence for GC in the general Italian population is estimated to be
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6 0.01% (31). Thus, the results of this study are in keeping with previous reports confirming that
7
8 AG is a condition at increased risk for gastric neoplasms (14).
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12 However, the Kaplan Meier curve shows that the majority of AG patients observed for a
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14 maximum of 16.5 years did not develop GNL, suggesting that a surveillance programme for all
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16 AG patients may be not cost-effective. A subset of AG patients at higher risk for GNL may be
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18 easily identified combining the cut-off of age together with two gastric histological parameters
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20 available at the time of AG diagnosis, potentially allowing to select those AG patients in whom
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22 the gastroscopic/histologic surveillance may be warranted.
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27 Regarding the role of *H pylori* infection on progression to GNL in AG patients, we used the
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29 Giemsa stain and the serology for the determination of the bacterium. In fact, other noninvasive
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31 tests, such as C-urea breath test and stool antigen test, seem to have a low diagnostic accuracy in
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33 this particular clinical setting (32). AG patients with incident GNL were not different from those
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35 without for the positivity of *H pylori* at baseline and the rate of eradication (data not shown).
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37 From our data, the effect of *H pylori* on progression rate to GNL in AG patients does not seem
38
39 important. This finding is in keeping with a previous large prospective study, which had
40
41 demonstrated that *H pylori* eradication may be beneficial in arresting the progression to GNL
42
43 only in patients without AG or intestinal metaplasia (33). However, we did not design a
44
45 randomized prospective study to evaluate the role of *H pylori* eradication on prevention of GC,
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47 and so, we cannot know if the obtained rate of GNL was influenced by eradication therapy.
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53 In the present cohort study, the AG patients were referred to a single-center, the protocol used
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55 for gastroscopy was the same for each patient, gastric biopsies were systematically taken in the
56
57 same location and were evaluated by updated Sydney System. Moreover, each patient was
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59 carefully informed about the need of endoscopic follow-ups, and the participation rate of AG
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patients at follow-up was as high as 74%. While the results of this study seem to be generally

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3 valid, they should be interpreted with caution. The overall number of observed case-findings of
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5 GNL was small, thus limiting the power of statistical analysis. The relative large confidence
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7 intervals observed in our Cox-regression are indicators of this problem. The feasibility of
8
9 longitudinal cohort studies involving a larger number of case-findings is difficult due to the low
10
11 overall prevalence of AG in the general population and the relatively low annual incidence rate
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13 of GNL. Regarding the concern about the study power, significance tests were performed to
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15 compare the prevalence of GNL in the presence of a risk factor, with that among patients
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17 without the risk factor. Because the present is a cohort study, the power of these comparisons
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19 was not calculated when the study was designed because there was little evidence to suggest the
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21 likely magnitude of the effects of the risk factors or their prevalence. *A posteriori*, on the basis of
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23 our observed data, the study power for age >50 years, atrophic pangastritis and severe body
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25 intestinal metaplasia could be calculated as 73.6%, 71.4% and 13%, respectively. This low
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27 power for intestinal metaplasia as risk factor could be explained by the fact that this feature was
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29 only found in less than half of the GNL patients, so a surveillance programme based on solely
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31 this entry criterion would miss more than half the cases. External validation of these risk factors
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33 on prospective case-series would be needed.

34
35 In conclusion, this study shows that AG patients who are over 50 years of age or who have
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37 atrophic pangastritis or severe body intestinal metaplasia seem to be at higher risk for developing
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39 gastric neoplastic lesions. This finding suggests that, in this subset of AG patients, an
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41 endoscopic-histological follow-up for GC surveillance may be worthwhile.

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35 LEGEND TO FIGURES

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37 **Figure 1:** Study population.

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40 **Figure 2:** Kaplan-Meier Analysis: Intervals between initial diagnosis of atrophic gastritis and
41 diagnosis of gastric neoplastic lesions. Proportion of patients with atrophic gastritis who
42 remained free of gastric neoplastic lesions.
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47 **Figure 3:** □ absent ■ mild ■ moderate ■ severe. Comparison of baseline atrophy and intestinal
48 metaplasia scores according to Sydney System between AG patients who developed GNL and
49 who did not. **a.** Atrophy of the body; **b.** Intestinal Metaplasia of the body, *p=0.0016 vs other
50 group; **c.** Atrophy of the antrum *p=0.0001 vs other group, **p=0.001 vs other group; **d.**
51 Intestinal Metaplasia of the antrum *p=0.0004 vs other group.
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Table 1: Patients with atrophic gastritis who developed neoplastic lesions during the follow-up

Age /gender patients	Macroscopic Lesions	Localization	Histology	Intervention	Neoplastic Lesions during follow-up	Outcome
51 F	Normal mucosa	Body	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
56 M	multiple polyps of 0.5 cm	Body	Low grade dysplasia	monitoring	Not recurrence	Free of Neoplastic lesions
66 F	Normal mucosa	Antrum	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
65 M	Normal mucosa	Antrum	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
57 M	Normal mucosa	Antrum	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
51 M	Ulcer	antrum	Intestinal adenocarcinoma	gastrectomy		
68 F	Normal mucosa	antrum	Low grade dysplasia	monitoring	Not recurrence	Free of Neoplastic lesions
68 M	Normal mucosa	antrum	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
55 M	Normal mucosa	body	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
71 F	Normal mucosa	antrum	Low grade dysplasia	monitoring	Confirmed dysplasia	Free of Neoplastic lesions
51 F	Multiple polyps of 0.2-0.4 cm	body	Low grade dysplasia	polypectomy		Intestinal adenocarcinoma [^]
57 M	Single polyp of 3 cm	antrum	high grade dysplasia	polypectomy	Recurrence dysplasia	Free of neoplastic lesions
54 F	Single polyp of 0.7 cm	antrum	Low grade dysplasia	polypectomy	Recurrence dysplasia	Free of neoplastic lesions
77 F	normal mucosa	antrum	Low grade dysplasia	monitoring	progression	Intestinal adenocarcinoma [§]

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3 ^ adenocarcinoma and two areas of high grade dysplasia were found on antral mucosa. Patient performed gastrectomy and nowadays is alive.

4 § a focus of adenocarcinoma and two areas of high grade dysplasia on normal mucosa were found at 12 months. Patient performed gastrectomy
5 and died for complications post-surgery
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Table 2: Risk Factors for Progression for Gastric Neoplastic Lesions in Univariate and Multivariate Cox Regression Analysis

Baseline	Overall progression to Gastric Neoplastic Lesions			
	HR univariate	95% CI	HR multivariate	95% CI
Gender	1.0		1.0	
Male	2.1	0.9 – 5.0	1.5	0.6-3.9
Female				
Age	1.0		1.0	
<50 years	14.0	1.9 – 102.3	8.8	1.2 – 68.4
>50 years				
Pattern of gastric atrophy	1.0		1.0	
Corpus-restricted atrophy	6.1	2.8 – 13.4	4.5	1.5 – 14.1
Atrophic pangastritis				
Gastric body intestinal metaplasia	1.0		1.0	
Absent, mild and moderate	4.5	1.8 – 11.0	4.0	1.3 – 11.8
Severe				
Gastric antrum intestinal metaplasia	1.0		1.0	
Absent	5.9	2.4-14.2	1.2	0.4 – 4.0
Present (mild, moderate, severe)				
OLGA system staging	1.0		1.0	
Stage I, II, III	5.5	1.6 – 18.8	0.8	0.2-3.7
Stage IV				
Pernicious anaemia	1.0		1.0	
Absence	1.1	0.5 – 2.7	0.6	0.2-2.0
Presence				
<i>H pylori</i> infection	1.0		1.0	
Negative	1.1	0.5 – 2.7	1.0	0.4-2.6
Positive				

Significant risk factors are in bold typeface.

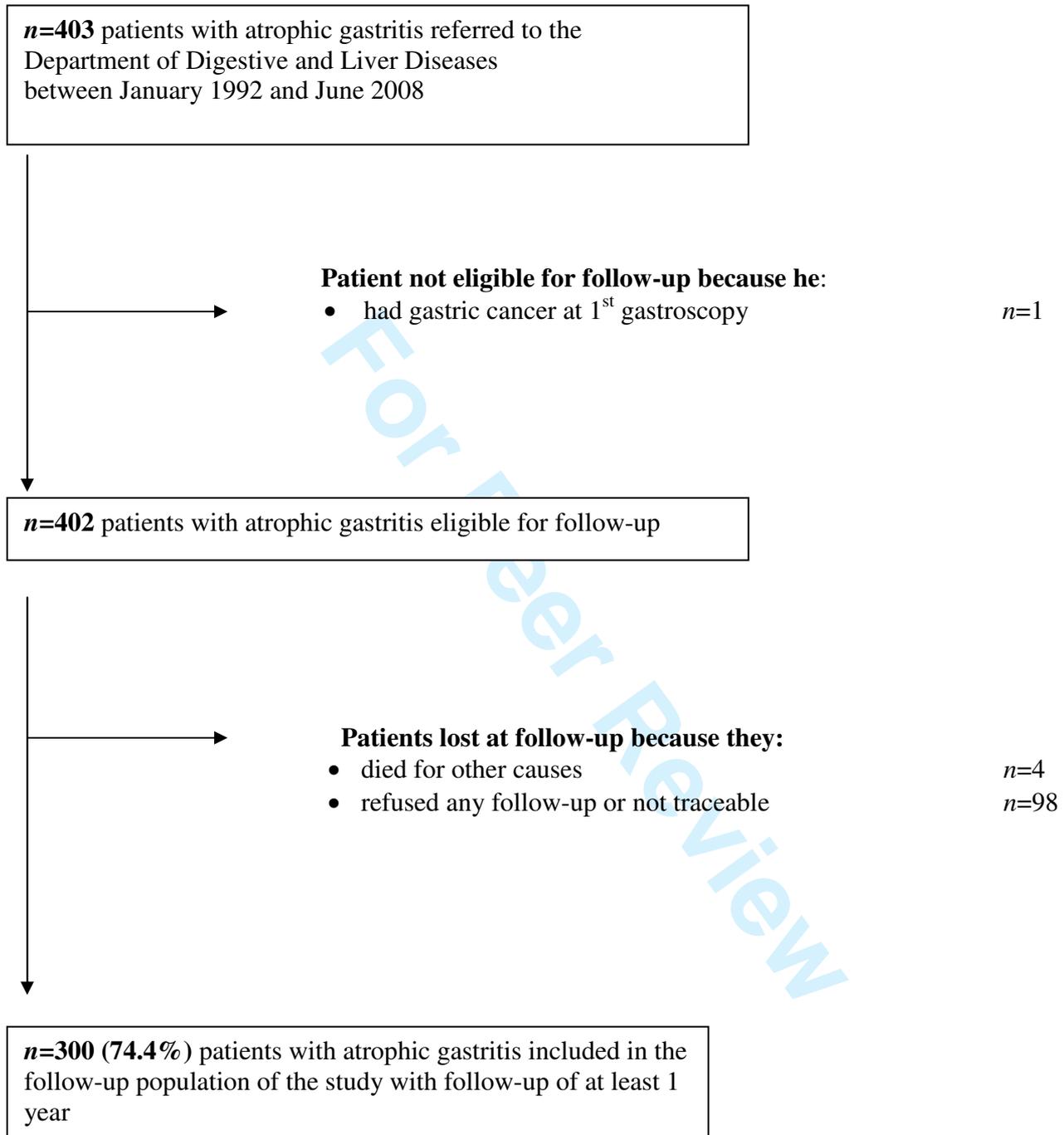
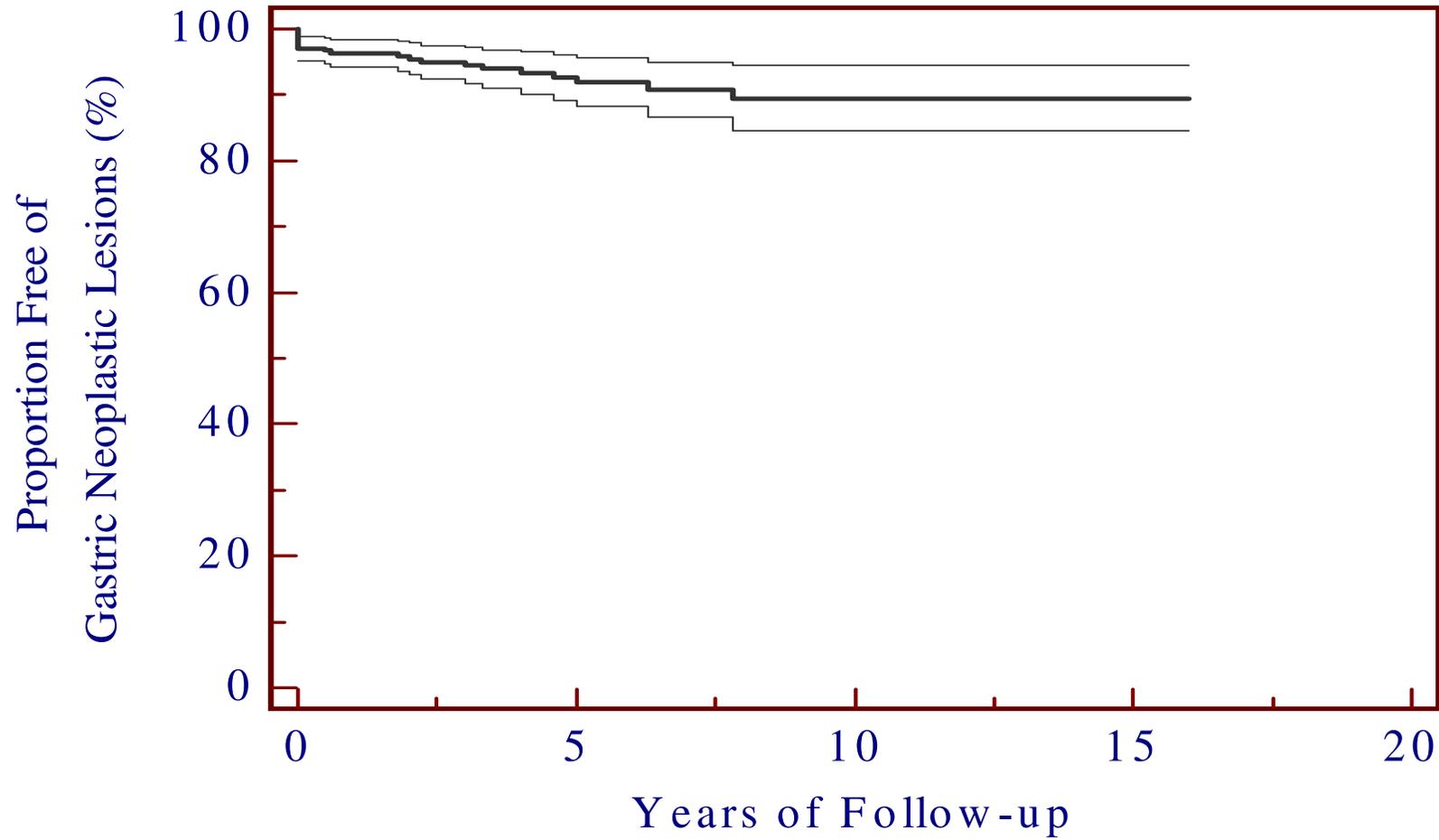
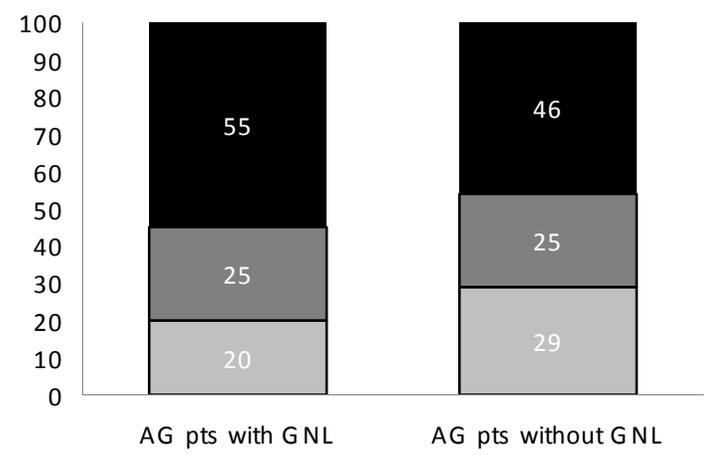


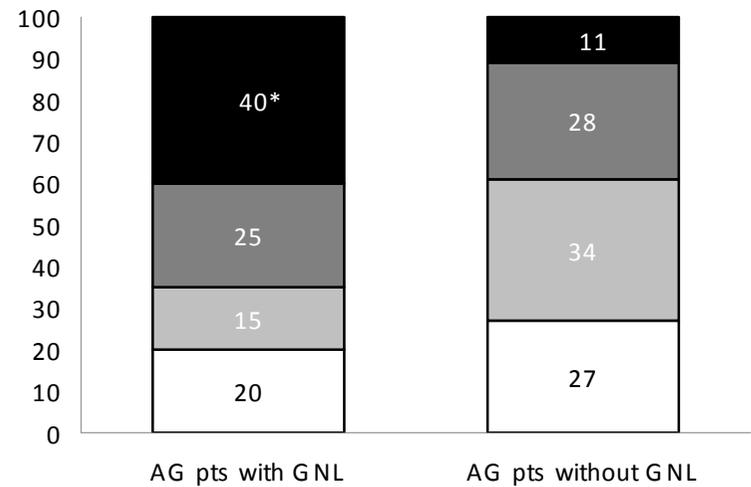
Figure 1

**Figura 2**1
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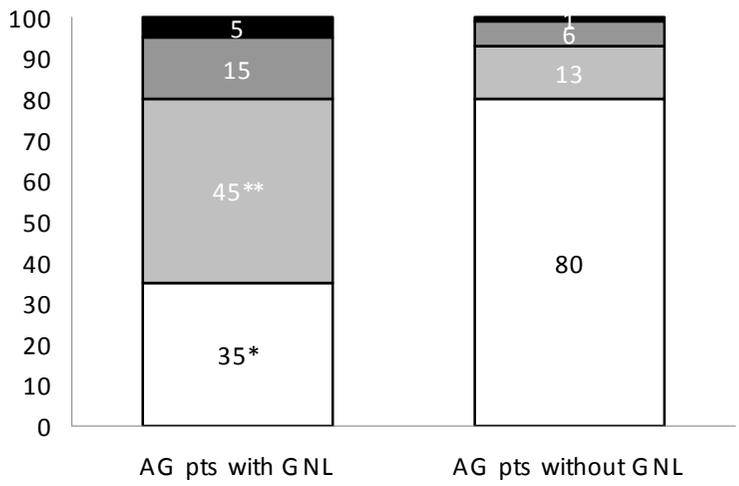
a Atrophy of the body



b Intestinal Metaplasia of the body



c Atrophy of the antrum



d Intestinal Metaplasia of the antrum

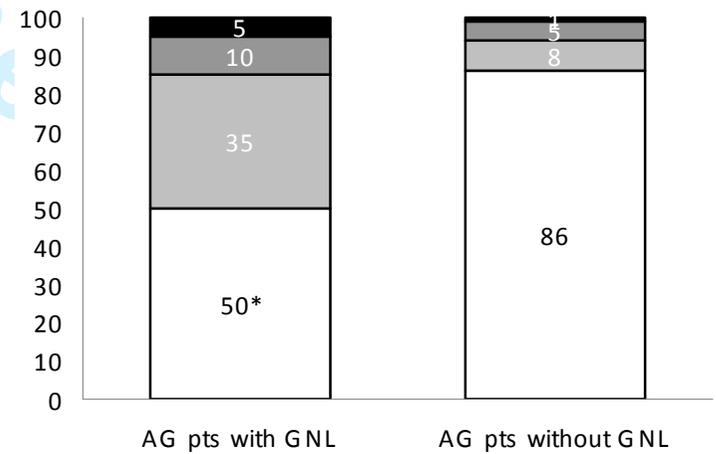


Figure 3

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