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Late response to nalfurafine hydrochloride for pruritus in patients with chronic liver disease: a retrospective data analysis

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Abstract

Background: Nalfurafine hydrochloride is used for refractory pruritus; however, real-world data on its efficacy with long-term administration, particularly in late responders who initially failed treatment, are limited. We aimed to evaluate the efficacy of nalfurafine hydrochloride in patients with chronic liver disease and clarify the incidence and characteristics of late responders.

Methods: A retrospective analysis of data of 210 patients who received nalfurafine hydrochloride for chronic liver disease-associated pruritus at our hospital since June 2015 was conducted. Efficacy at 12 weeks was evaluated in 76 patients for whom visual analog scale (VAS) assessment was possible.

Results: Among all 76 patients, the VAS score significantly decreased from 55.2 before treatment to 30.0 after 12 weeks ($P<0.001$), resulting in an efficacy rate of 48.6%. The efficacy was generally consistent across analyses according to underlying liver disease and presence and stage of hepatocellular carcinoma. Of the 39 patients who were nonresponders at 12 weeks, 30 continued treatment until 48 weeks. Seven of these 30 (23%) patients experienced improvement in pruritus at 48 weeks and were defined as late responders.

Conclusions: The study findings suggest the importance of considering continued treatment under careful follow-up, rather than discontinuing treatment based solely on initial response.

BACKGROUND

Skin pruritus associated with chronic liver disease is a common symptom in patients with primary biliary cholangitis (PBC), liver cirrhosis, and chronic hepatitis; it is a substantial clinical problem that impactfully reduces patients' quality of life (QOL). Skin pruritus has been reported to cause insomnia, depression, anxiety, and impaired activities of daily living [1, 2]; moreover, in severe cases, it can seriously impact treatment continuation and social life. However, pruritus severity does not necessarily correlate with the degree of liver dysfunction [3]; furthermore, its pathogenesis remains incompletely understood.

The pathogenesis of pruritus in patients with chronic liver disease is thought to involve a complex combination of factors, including bile acid accumulation, increased opioidergic tone, lysophosphatidic acid, and increased autocrine motility factor (autotaxin) that catalyzes the production of lysophosphatidic acid as a potent pruritogen [4]. Traditionally, antihistamines, cholesteatomatics, and rifampicin have been used for treatment. However, in many cases, they proved ineffective; moreover the side effects and safety of their long-term use remain questionable [5].

Against this background, nalfurafine hydrochloride (Remitch®; TORAY Industries, Inc., Tokyo, Japan), a kappa opioid receptor agonist, has garnered attention as a new treatment option for ameliorating pruritus by targeting kappa opioid receptors expressed on neurons within the central nervous system. Nalfurafine hydrochloride is covered by health insurance for the treatment of refractory pruritus associated with chronic liver disease; its effectiveness has been suggested, even in cases, wherein

traditional treatments have been insufficiently effective [6]. Furthermore, it is characterized by relatively little mu-opioid receptor-mediated addictive or sedative effects [7]. However, to date, there are still insufficient clinical data on the efficacy and safety of long-term administration of nalfurafine hydrochloride in patients with chronic liver disease. The differences in treatment responses based on disease background and severity of pruritus warrant further investigation.

In this study, we aimed to clarify the long-term clinical efficacy and usefulness of nalfurafine hydrochloride for treating pruritus in patients with chronic liver disease. Furthermore, even if nalfurafine hydrochloride was ineffective at 12 weeks after treatment initiation, long-term continuation of nalfurafine hydrochloride therapy showed efficacy at 48 weeks. We defined these as late responders and assessed their frequencies and characteristics.

METHODS

Patients and analytical methods

We retrospectively analyzed 210 patients who received nalfurafine hydrochloride for pruritus associated with chronic liver disease at our hospital since June 2015. Of these, 76 patients who were able to be assessed using a visual analog scale (VAS) were included in the analysis to assess efficacy at 12 weeks. Efficacy was defined as a VAS reduction of 25 mm or greater. Furthermore, among patients who were ineffective at 12 weeks, late responders who continued treatment up to 48 weeks were analyzed.

Statistical analysis

Comparisons between two groups were performed using Student's T test and Fisher's exact test, with $p < 0.05$ considered significant.

RESULTS

Patient background and study design

In total, 210 patients treated with nalfurafine hydrochloride for pruritus associated with chronic liver disease at Kinki University Hospital since June 2015 were evaluated. The underlying liver diseases were hepatitis C (HCV) in 91 patients (43.3%), non-B, non-C, unknown cause (NBNC) in 34 patients (16.2%), alcoholism in 24 patients (11.4%), hepatitis B (HBV) in 22 patients (10.5%), metabolic dysfunction-associated steatohepatitis (MASH) in 12 patients (5.7%), autoimmune hepatitis (AIH) in 9 patients (4.3%), PBC in 9 patients (4.3%), and other conditions in 11 patients (5.2%) (Figure 1). Of the 210 patients, 76 were evaluated for efficacy using a VAS. The efficacy of nalfurafine hydrochloride was compared after 12 weeks. Thirty-seven patients were responders and 39 were non-responders (Figure 2). A reduction in the VAS score of 25 mm or more was defined as effective. The VAS score was calculated based on the most severe pruritus observed during the day. In this analysis, the dose of nalfurafine

hydrochloride was 2.5 μg/day in 74 patients (97%) and 5.0 μg/day in 2 patients (3%). None of the patients required an increase in the dose from 2.5 μg/day to 5.0 μg/day.

Efficacy at week 12

Comparing all 76 patients, the VAS score at week 12 significantly decreased from 55.2 to 30.0 (P<0.001), showing an efficacy rate of 48.6% (Figure 3). Comparing patient characteristics according to efficacy and non-efficacy, no significant differences were found in age, sex, Child–Pugh grade, presence or absence of hepatocellular carcinoma (HCC), Fibrosis-4 (FIB-4) index score, or hepatic and renal functions (Table 1).

Table 1. Patient characteristics by response assessment at 12 weeks

	Responder (n=37)	Non responder (n=39)	p value
Age (years)	71±10	73±9	0.39
Sex (male/female)	22/15	23/16	1
Child–Pugh grade(A/B)	26/11	32/7	0.28
HCC (yes/no)	14/23	12/27	0.62
FIB4 index (≥3.25/<3.25)	24/13	27/12	0.80
AST (U/L)	47±32	41±28	0.41
ALT (U/L)	39±42	30±26	0.30
ALP (U/L)	356±181	401±292	0.42
γGTP (IU/L)	64±68	90±140	0.30
T-bil (mg/dL)	0.9±0.3	0.8±0.4	0.85
ALB (g/dL)	3.6±0.5	3.7±0.5	0.76
eGFR (mL/min/1.73 m^2)	61±25	65±23	0.52

HCC, Hepatocellular Carcinoma; FIB4 index, Fibrosis-4 Index; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline Phosphatase; □GTP, Gamma-glutamyl transferase; T-bil, Total bilirubin; ALB, Albumin; eGFR, Estimated glomerular filtration rate

Next, the efficacy of nalfurafine hydrochloride was compared by underlying liver disease. A decrease in the VAS scores was confirmed for all diseases, including HBV, HCV, MASH, alcohol, AIH, PBC, and NBNC, demonstrating its efficacy (Figure 4a, b).

The efficacy was evaluated based on the presence or absence of HCC. Of the 76 patients (34.2%), 26 had HCC (Figure 5). Evaluation was also performed according to HCC stage, demonstrating efficacy even in advanced stages (Figure 6a, b).

Evaluation of late responders

Of the 39 patients in whom nalfurafine hydrochloride was ineffective after 12 weeks, 30 continued treatment with nalfurafine hydrochloride until week 48. Of these 30 patients, seven (23%) showed drug efficacy at week 48 (Figure 7). These patients were identified as late responders. To characterize late responders, pretreatment factors were compared; however, no significant factors were determined (Table 2). Furthermore, performing analysis of the underlying liver disease, no liver disease was found to predispose patients to late response (Figure 8).

Table 2. Characteristics of late responders (pretreatment factors)

	Non response (n=23)	Late response (n=7)	p value
Age (years)	73±11	75±4	0.61
Sex (male/female)	15/8	3/4	0.39
Child–Pugh grade (A/B)	19/4	7/0	0.54
HCC (yes/no)	5/18	3/4	0.34
FIB4 index (≥3.25/<3.25)	15/8	3/4	0.39
AST (U/L)	40±32	34±17	0.67
ALT (U/L)	26±18	34±25	0.35
ALP (U/L)	401±337	428±305	0.84
γGTP (IU/L)	95±160	118±164	0.74
T-bil (mg/dL)	0.8±0.3	0.6±0.2	0.31
ALB (g/dL)	3.7±0.5	3.7±0.6	0.70
eGFR (mL/min/1.73 m^2)	62±20	78±32	0.12

HCC, Hepatocellular Carcinoma; FIB4 index, Fibrosis-4 Index; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline Phosphatase; GTP, Gamma-glutamyl transferase; T-bil, Total bilirubin; ALB, Albumin; eGFR, Estimated glomerular filtration rate

DISCUSSION

In this study, we retrospectively evaluated the efficacy of nalfurafine hydrochloride, a kappa-opioid receptor agonist, for the treatment of pruritus associated with chronic liver disease at 12 weeks. The results revealed that among 76 patients, the VAS score significantly decreased from 55.2 before treatment to 30.0 after 12 weeks, representing an efficacy rate of 48.6%. These results suggest that nalfurafine hydrochloride is clinically useful for treating refractory pruritus in patients with chronic liver disease.

An analysis comparing patient characteristics according to efficacy and non-efficacy revealed no significant differences in age, sex, Child–Pugh grade, presence or absence of HCC, FIB-4 index score, or liver or kidney function indices. This suggests that the pruritus-relieving effect of nalfurafine hydrochloride might not be significantly dependent on background factors, such as hepatic reserve, degree of fibrosis, or the presence or absence of tumors. Although concerns about the therapeutic efficacy and safety have traditionally been raised in patients with impaired liver function or advanced liver disease, the results in this study suggest that this agent might be useful for managing patients with a wide range of chronic liver disease conditions. Furthermore, analysis of the underlying liver disease confirmed a decrease in VAS scores for all diverse causes, including HBV, HCV, MASH, alcoholic liver disease, AIH, PBC, and NBNC. Although pruritus associated with chronic liver disease is commonly associated with cholestatic disease, it has also been reported to occur at a certain frequency in cases of non-cholestatic diseases [3]. The results in this study support the possibility that the kappa-opioid receptor system might be commonly involved in pruritus across a variety of liver diseases thought to have different causes, suggesting the general applicability of the mechanism of action of nalfurafine hydrochloride.

Performing an analysis focusing on patients with HCC (Akuta), 34.2% of patients had HCC; moreover, pruritus improvement was observed in patients with HCC, similar to that in individuals without HCC. A Japanese study also reported no difference in the efficacy between patients with and without HCC [8]. In our study, we further analyzed HCC stage; of note, efficacy was maintained even in advanced stages. Although supportive therapy is often ineffective in patients with advanced HCC due to poor general health and concomitant treatment, the results in this study demonstrated that symptomatic relief from pruritus could be expected even in patients with advanced HCC. This is considered clinically significant from the perspective of improving QOL.

In this study, we administered nalfurafine hydrochloride to treat pruritus associated with chronic liver disease and investigated whether there were any cases of delayed response to long-term treatment (late responders) among patients in whom the treatment was deemed ineffective at 12 weeks. Of the 39 patients in whom treatment was ineffective at 12 weeks, 30 continued it until 48 weeks; seven of these 30 (23%) showed improvement in pruritus at 48 weeks. This suggests that even in cases of poor initial responses, approximately one-quarter of patients might achieve therapeutic benefits with long-term administration. To clarify the characteristics of late responders, we compared pretreatment factors, such as age, sex, etiology of liver disease, hepatic reserve, FIB-4 index score, and hepatic and renal function; however, no significantly associated factors were identified. Furthermore, examination of patients with

underlying liver disease did not reveal any tendency for specific liver diseases in late responders. These results suggest that the delayed effects of nalfurafine might be difficult to predict, at least based on general clinical background factors.

Nalfurafine acts as a kappa-opioid receptor agonist in the central nervous system and is thought to suppress pruritic hypersensitivity [7, 9]. The onset and persistence of pruritus are thought to be related to multiple factors, including changes in the opioid receptor balance, inflammatory cytokines, bile acids, and neuroplasticity [10–12]. Changes in these pathological conditions over time might delay the onset of treatment response. The finding of a certain percentage of late responders in this study suggests that the pathological condition of pruritus is not fixed and might be gradually modified with long-term treatment. Clinically, even if there is no clear improvement at 12 weeks or tolerability concerns and patient wishes to continue treatment, continuing nalfurafine administration for a certain period rather than discontinuing it prematurely might be useful. However, since no factors capable of predicting late responders were identified, this does not justify long-term administration without careful consideration. Careful follow-up is required, considering symptom progression, QOL, and comorbidities.

The limitations of this study include its retrospective nature and the limited number of cases, particularly the absolute number of late responders. Furthermore, since the study was limited to patients who were able to continue treatment for 48 weeks, the influence of selection bias cannot be ruled out. Furthermore, considering that pruritus assessment was a subjective measure by a VAS and the effects of concomitant treatment and lifestyle factors were not fully evaluated is important. Future studies and analyses incorporating biological markers are needed to clarify the predictors of late response and optimal duration of treatment.

CONCLUSIONS

Treating pruritus associated with chronic liver disease with nalfurafine hydrochloride, a late response was observed in approximately 23% of the patients, even among those in whom treatment deemed ineffective at 12 weeks. Although predicting late responders based on pretreatment factors was difficult, the presence of patients whose symptoms improved with long-term treatment could be an important finding for informing treatment strategies for managing pruritus.

Abbreviations

AIH, autoimmune hepatitis

HBV, hepatitis B

HCC, hepatocellular carcinoma

HCV, hepatitis C

MASH, metabolic dysfunction-associated steatohepatitis

NBNC, non-B, non-C, unknown cause

PBC, primary biliary cholangitis

QOL, quality of life

VAS, visual analog scale

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. Ethical approval was waived by the Institutional Review Board of Kindai University because the study used fully anonymized data and did not involve direct intervention with human participants. The requirement for informed consent was waived owing to the retrospective nature of the study, and an opt-out procedure was employed.

Consent for publication

Not Applicable

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy restrictions involving human participants but are available from the corresponding author on reasonable request, subject to approval by the relevant ethics committee.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: **SH:** Conceptualization, Methodology, Software, Supervision, Data curation, Writing- Original draft preparation. **SH, TM, NOm, NOk, YK, KU, YM, MT, MM, HC, NN, MK**: Visualization, Investigation. **MK**: Software, Validation. **NN:** Writing- Reviewing and Editing. All authors reviewed the text and approved the final version of the manuscript for publication.

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Figures

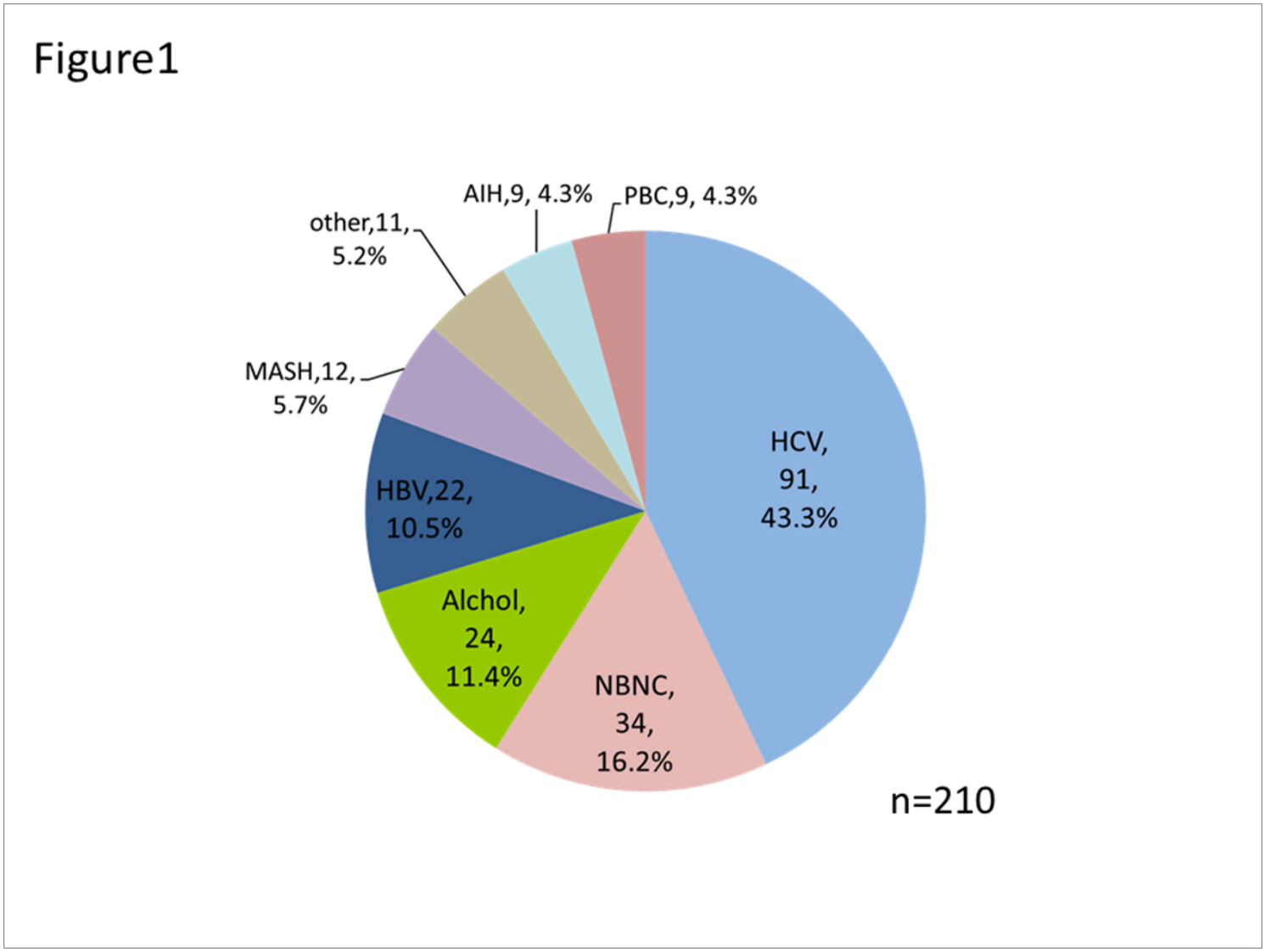


Figure 1

Breakdown of underlying liver disease. We evaluated 210 patients treated with nalfurafine hydrochloride for pruritus associated with chronic liver disease. The underlying liver diseases were hepatitis C in 91 (43.3%), NBNC in 34 (16.2%), alcoholism in 24 (11.4%), hepatitis B in 22 (10.5%), MASH in 12 (5.7%), AIH in 9 (4.3%), PBC in 9 (4.3%), and other conditions in 11 (5.2%) patients. Abbreviations: AIH, autoimmune hepatitis; MASH, metabolic dysfunction-associated steatohepatitis; NBNC, non-B, non-C, unknown cause; PBC, primary biliary cholangitis

Figure2

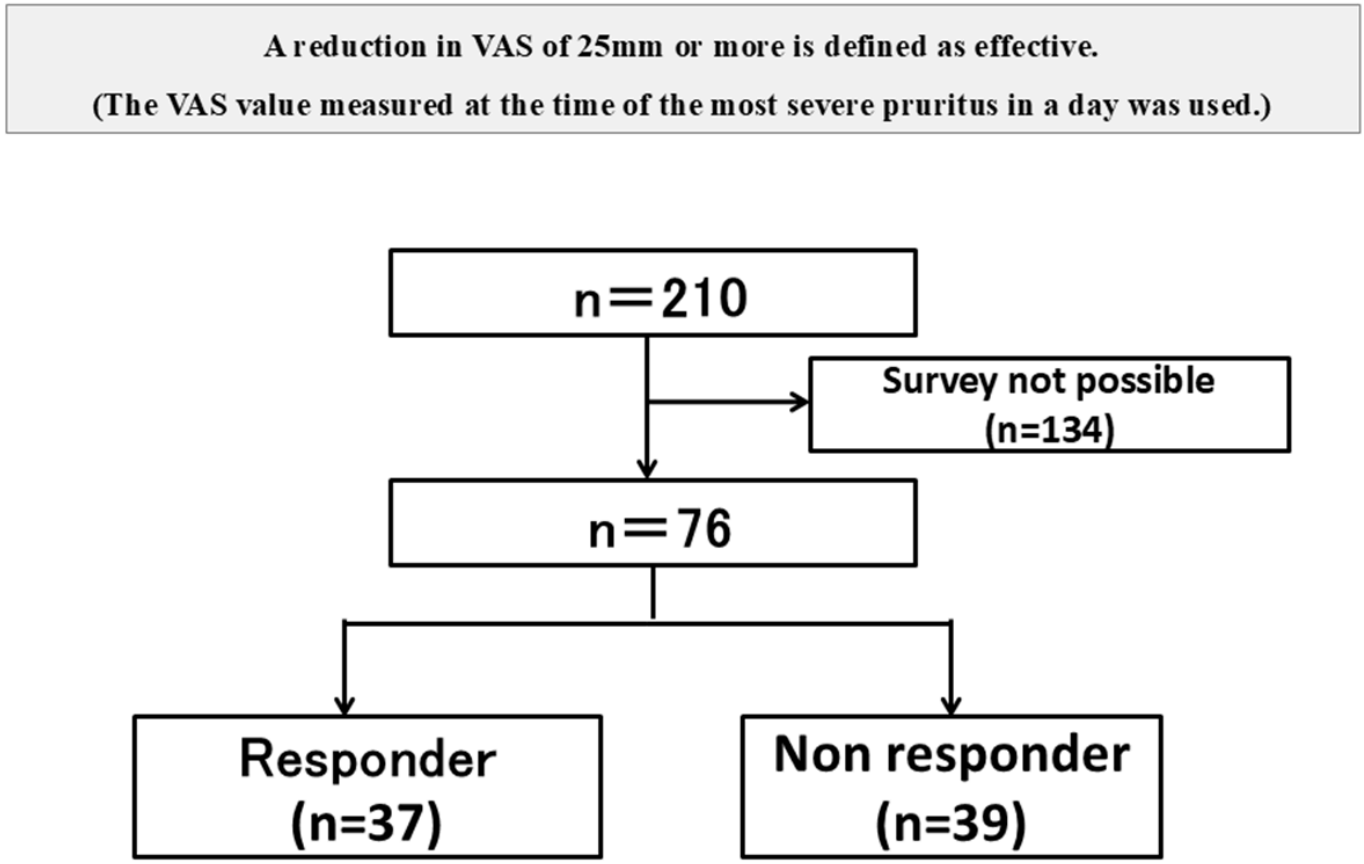


Figure 2

Study design. The efficacy of nalfurafine hydrochloride at 12 weeks was compared among the 76 patients whose VAS responses were assessed. Thirty-seven patients were responders and 39 patients were non-responders. The efficacy was evaluated 12 weeks after administration of nalfurafine hydrochloride; a VAS reduction of 25 mm or greater was defined as effective. The VAS score was calculated based on the most severe pruritus score on that day. Abbreviation:VAS, visual analog score

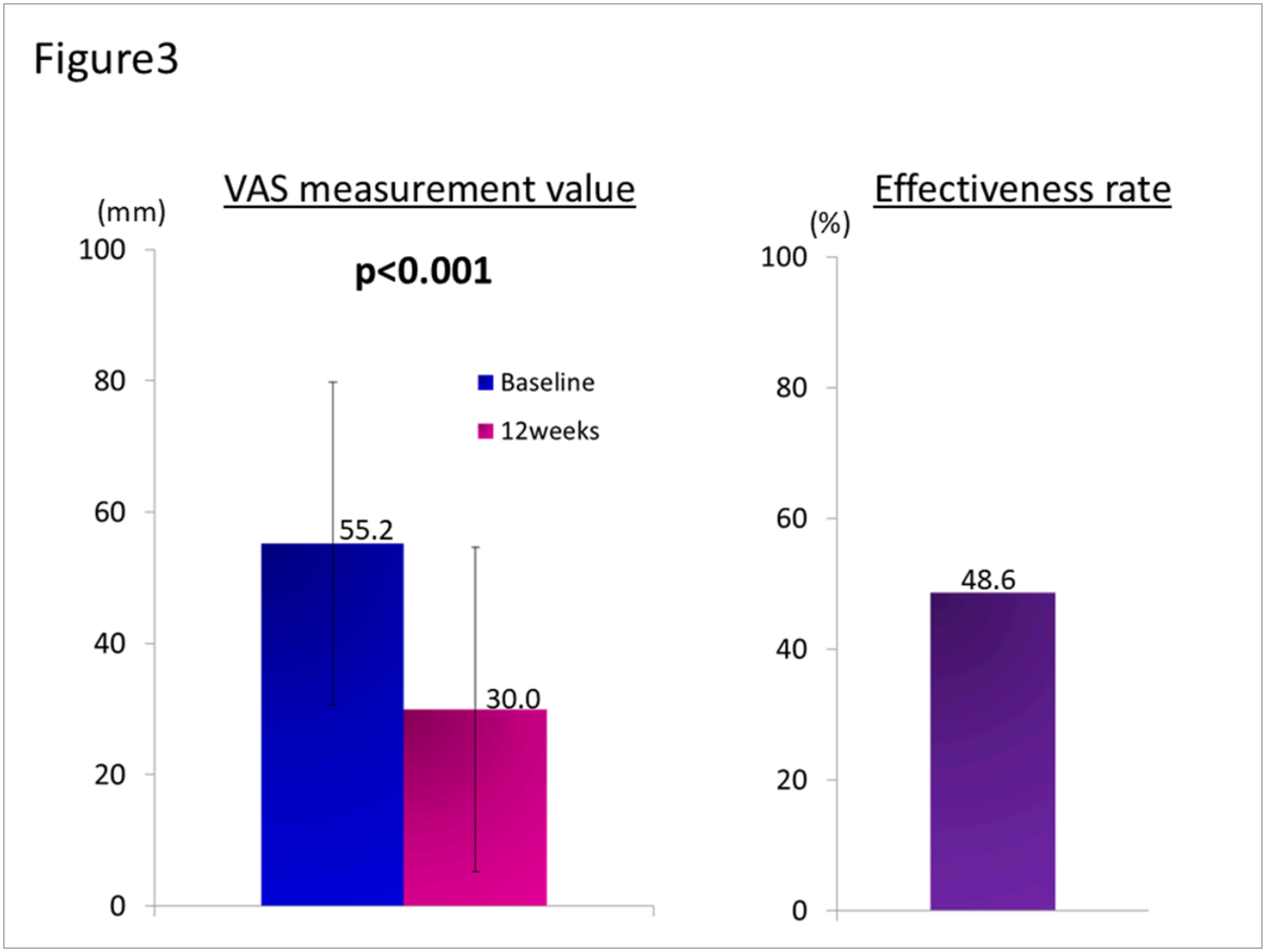


Figure 3

Efficacy at week 12 (overall). Comparing the 76 patients, the VAS score significantly decreased from 55.2 to 30.0 at week 12 (P<0.001), representing an efficacy rate of 48.6%. Abbreviation: VAS, visual analog score

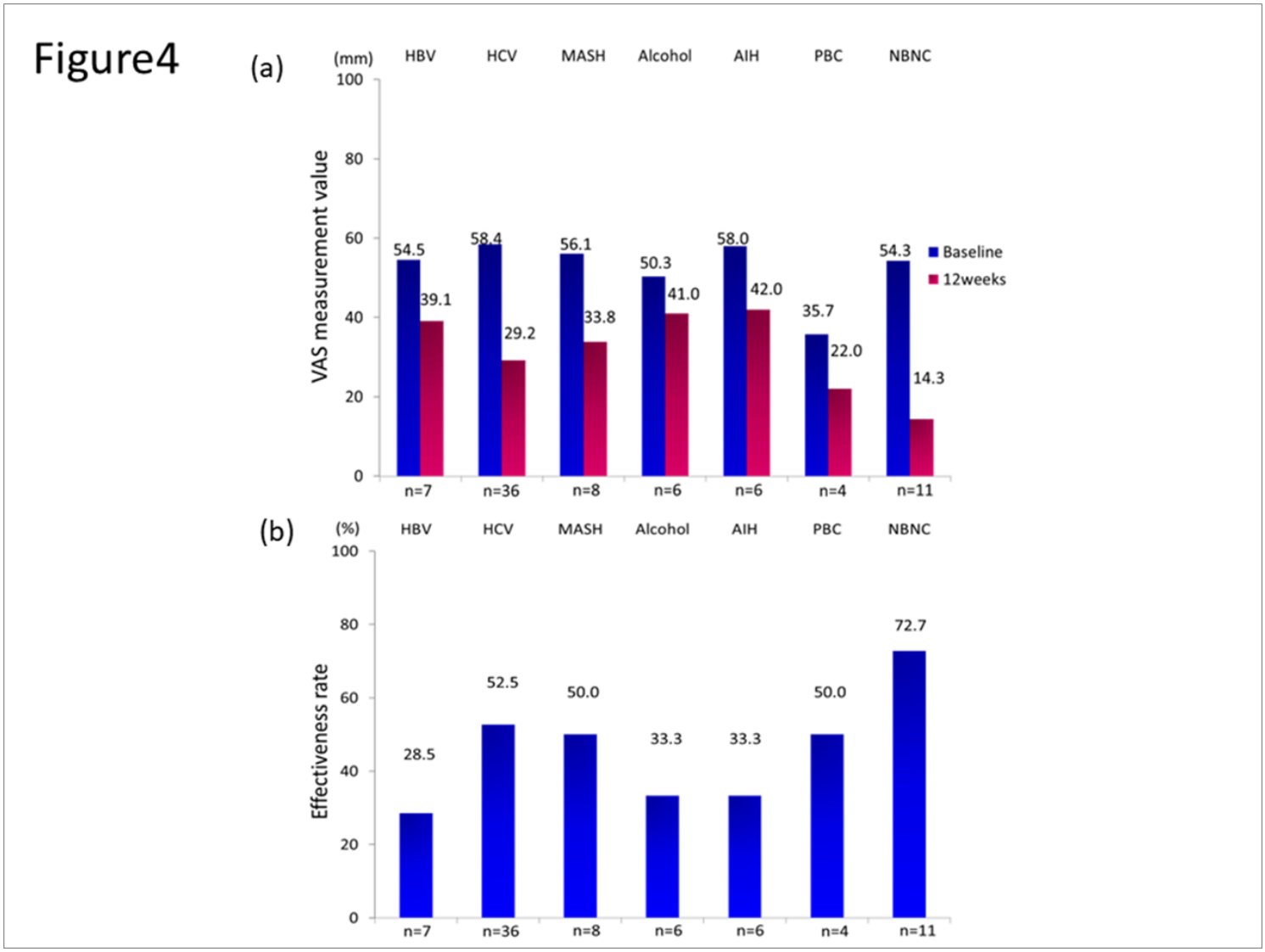


Figure 4

Efficacy at week 12 (By underlying liver disease). Decreases in the VAS scores were found in all patients with HBV, HCV, MASH, alcohol, AIH, PBC, and NBNC (of unknown etiology), demonstrating its efficacy. (a) VAS score; (b) efficacy rate (%). Abbreviations: AIH, autoimmune hepatitis; HBV, hepatitis B; HCV, hepatitis C; MASH, metabolic dysfunction-associated steatohepatitis; NBNC, non-B, non-C, unknown cause; PBC, primary biliary cholangitis; VAS, visual analog score

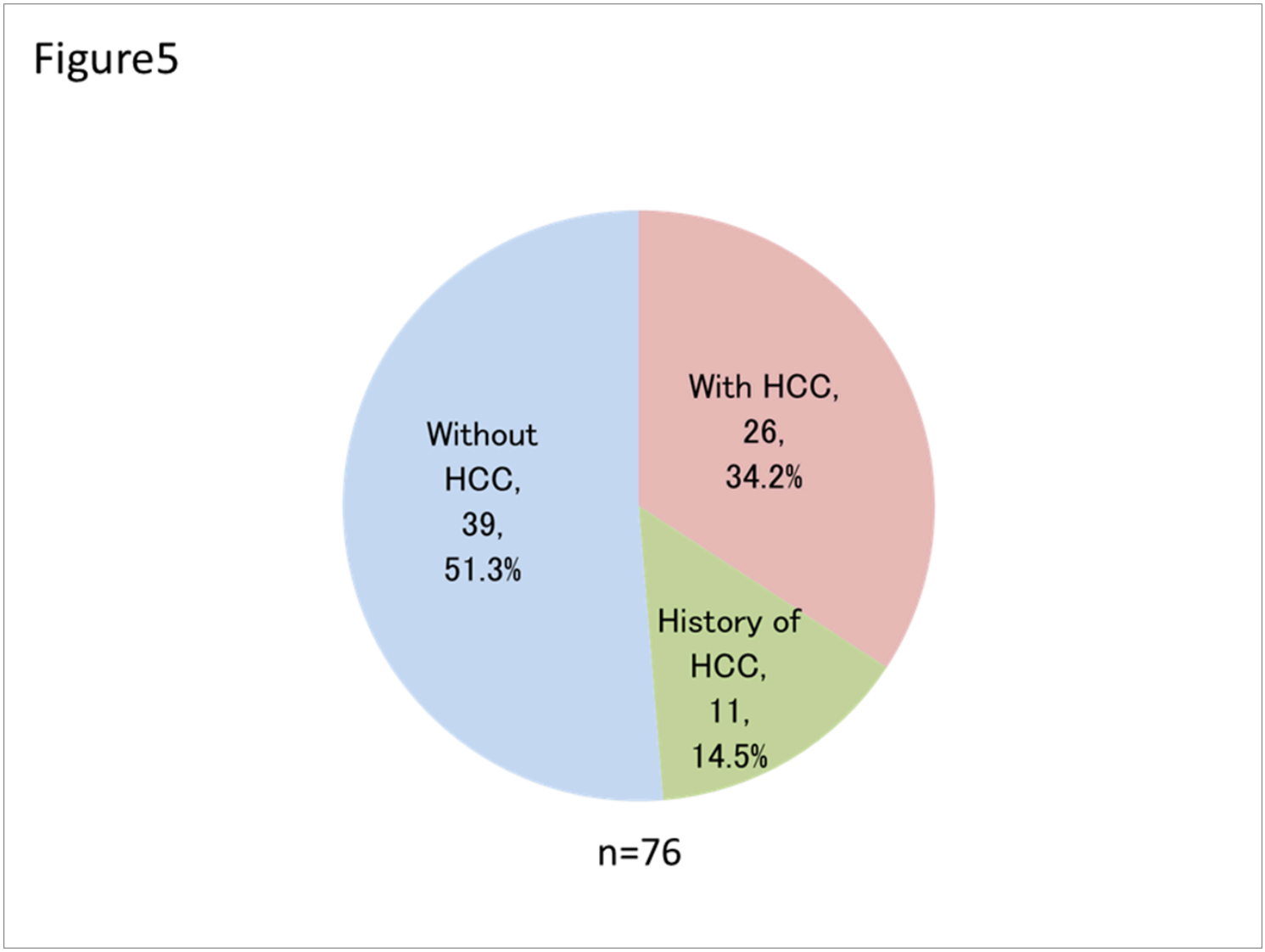


Figure 5

HCC incidence. Twenty-six of the 76 patients (34.2%) had HCC. Abbreviation: HCC, hepatocellular carcinoma

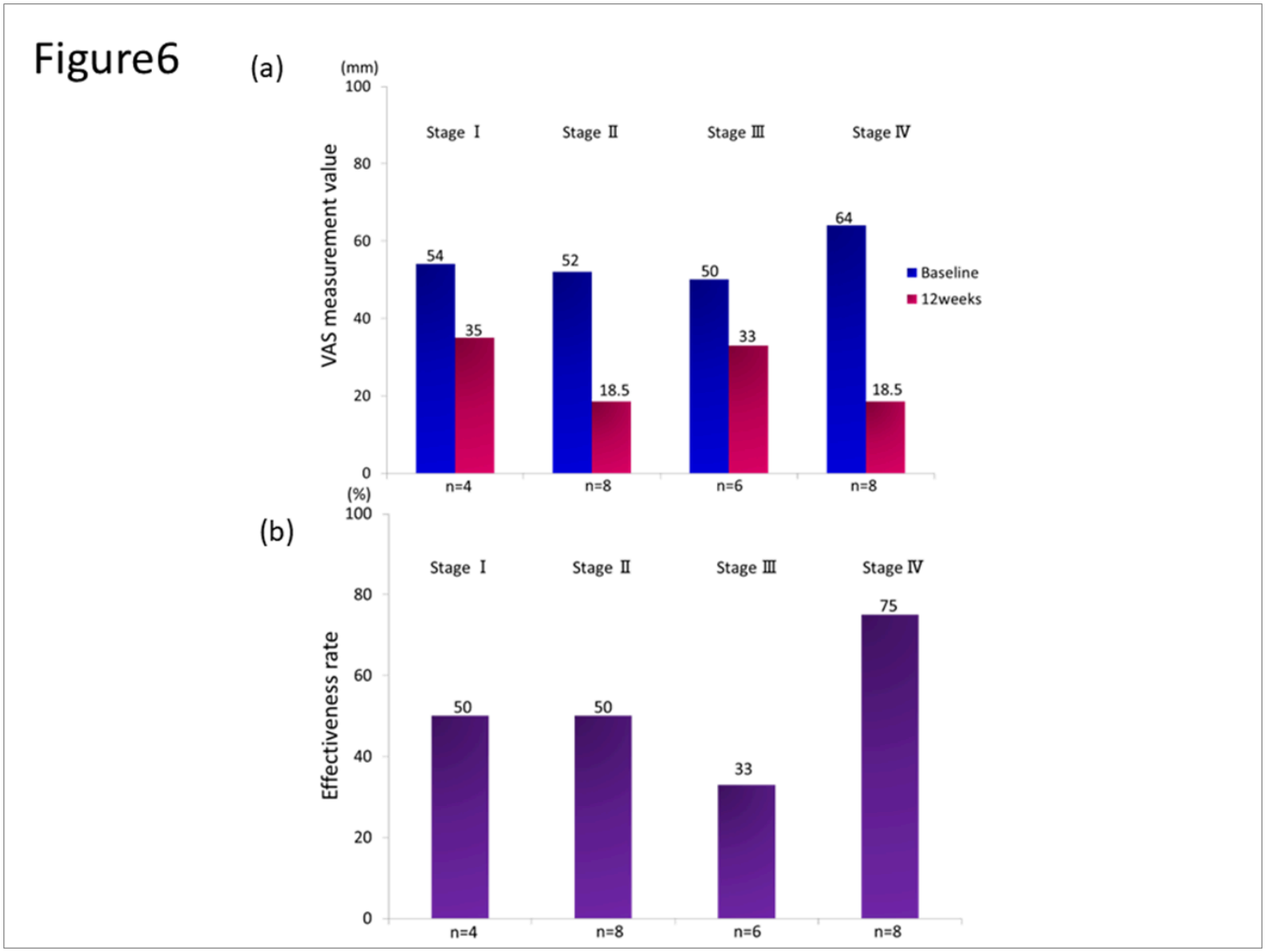


Figure 6

HCC stage. Efficacy was maintained even in the advanced stages of HCC. a) Actual VAS score (b) Efficacy rate (%).Abbreviations: HCC, hepatocellular carcinoma; VAS, visual analog score

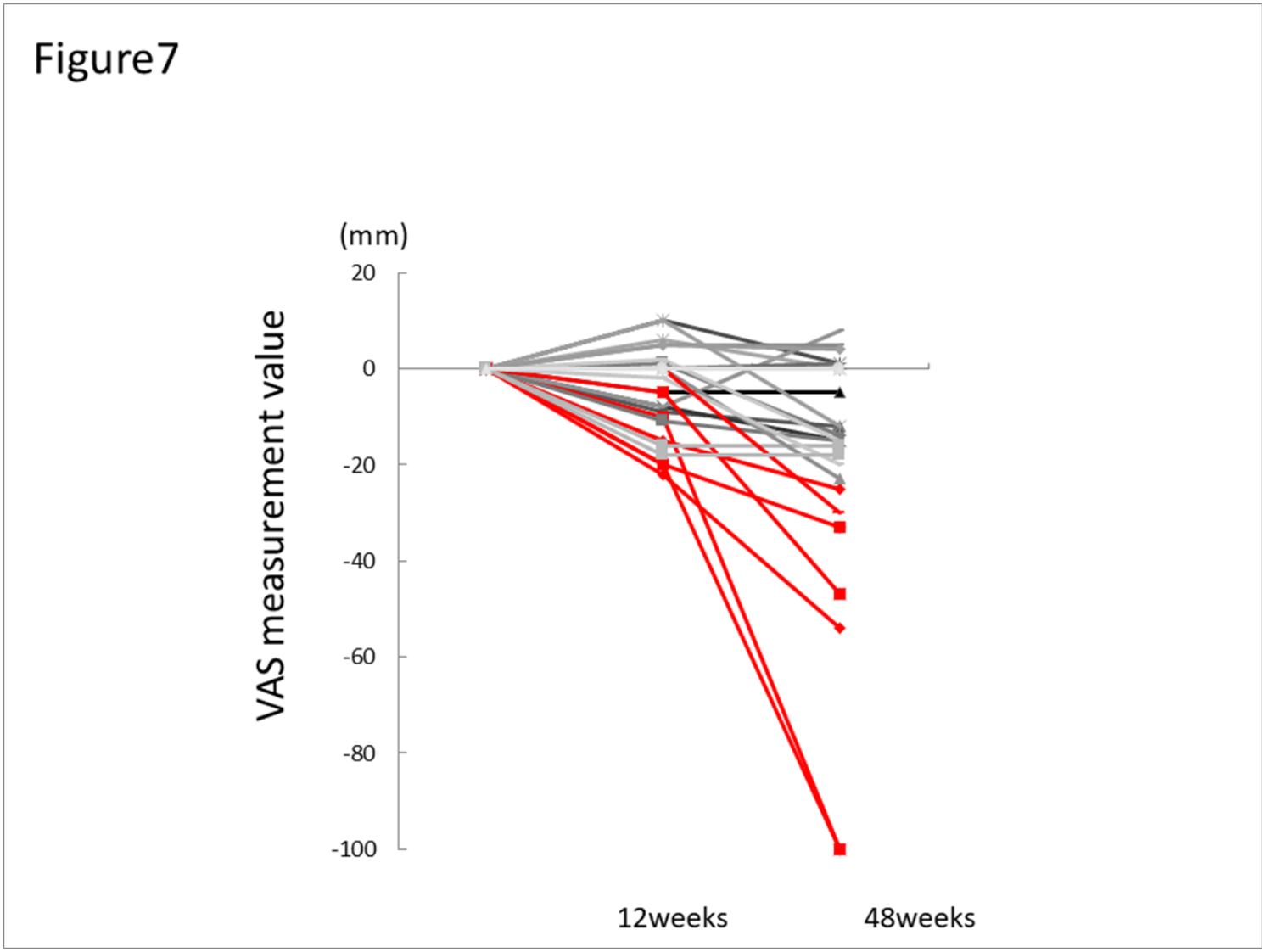


Figure 7

Evaluation of late responders. Of the 39 patients in whom nalfurafine hydrochloride treatment was ineffective after 12 weeks, 30 continued treatment with nalfurafine hydrochloride until week 48. Of these 30 patients, seven (23%) demonstrated drug efficacy at week 48.

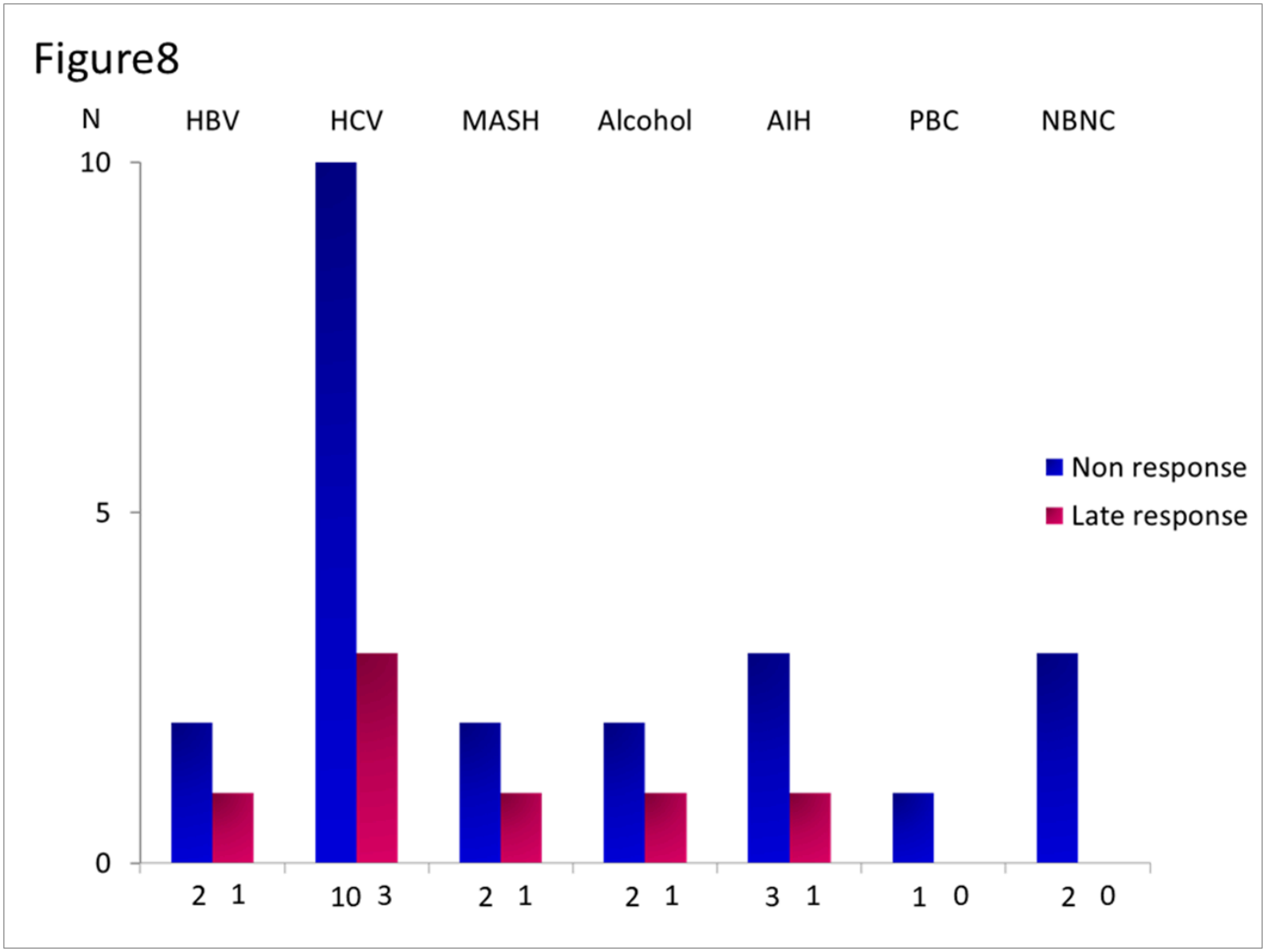


Figure 8

Analysis by underlying liver disease. No liver disease predisposing to late response was identified.