厚生労働科学研究費補助金（肝炎等克服政策研究事業）
令和元-３年度　総合研究報告書
肝炎ウイルス感染状況の把握及び肝炎ウイルス排除への方策に資する疫学研究

C 型肝炎ウイルス排除後患者の生命予後、肝細胞癌発生後の予後、通院状況、再感染の評価

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研究要旨

C 型肝炎ウイルス（HCV）感染症は、経口抗 HCV 薬（DAA）の登場により、飛躍的に HCV 排除達成例、いわゆる SVR 例が増加した。一方でこの増加した SVR 達成後の C 型肝炎患者の転帰についてはまだ不詳な点が多い。今回の研究で我々はまず SVR 症例のコホートを作成し、SVR 後の生存に対する SVR 前・HCV 持続感染時の肝細胞癌（HCC）根治治療施行既往の影響、肝硬変の影響を調査し、根治術後であっても HCC 既往は SVR 後の予後に大きく影響し生存率を下げること、一方で代償性肝硬変であれば SVR により肝硬変のない症例と同程度の生命予後が期待できることを示した。引き続き SVR 後に初発で発生した HCC 症例の声明予後を調査し、仮に SVR 後に HCC が発生しても、その予後は HCV 持続感染中（SVR 前）に発生した HCC 症例の生命予後に比し著明に改善していることを示し、これは SVR による肝機能の改善が主要因であることを示した。

一方、我が国においては一旦 SVR が達成されれば、その後も定期通院している症例では HCV の再感染は生じないことを確認した。しかし、SVR 後の定期通院継続率は SVR 後 HCC の発生リスクにもかかわらず低下していくこと、特に感染要因がかつての医療行為や輸血ではなく、今後も感染リスクのある行為での感染が疑われる症例に SVR 後通院 drop out 症例が多いことを示し、HCV 完全撲滅のためにはこれら症例への対策の必要性があることを示した。さらに、一般の日常医療において、SVR 症例では HCV の排除にもかかわらず HCV 抗体陽性が持続するために HCV 感染例と誤認される事象を一定の頻度で経験していることが示された。

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A. 研究目的

C 型慢性肝炎症例においては、直接作動型抗ウイルス薬（DAAs）の臨床使用により、ほぼ全例で C 型肝炎ウイルス（HCV）の排除（SVR）が可能となったが、SVR 後の経過・予後などについては未だ十分な知見がえられていない。今回の班研究・分担研究ではさまざまな視点からこれら SVR 症例のその後の経過を明らかにすることを目的とした。具体的には、

①SVR 達成までに HCV 持続感染により生じていた肝細胞癌（根治治療後）の既往や、代償性肝硬変が SVR 症例の生命予後に影響するか

②SVR 後に発生した HCC（再発を除く）症例の生命予後は HCV 持続感染中に発生した HCC 症例に比べて改善しているか、その理由は何か、

③SVR 症例はその後も HCC のサーベイランス目的に定期通院を続けているか、また SVR 後に HCV に再感染することはないのか、

④一般の日常診療において、SVR 症例は C 型肝炎「でない」症例として扱われているか、

の 4 点を中心に研究・調査を行った。

B. 研究方法

大垣市民病院及び多施設共同研究により上記①～④のテーマにつきそれぞれ調査を行った。すなわち、

①SVR 各症例の背景・合併症他の情報と HCC 既往・非代償性肝硬変の有無・予後を調査し、HCC 既往・代償性肝硬変の有無と生存率の関係を解析した（多施設共同研究）。

②SVR 後に発生した初発の HCC 症例の患者情報･HCC 進行度・肝機能・病理所見・再発率・生存率を、HCV 持続感染中に発生した初発 HCC（いわゆる C 型肝癌）と比較した（多施設共同研究）。

③大垣市民病院における SVR 症例のその後の通院状況を調査した。また SVR 確定後測定した HCV RNA が採用性になっている頻度を調査した（大垣市民病院単施設研究）。
④SVR 後通院継続例にアンケート調査を施行し、SVR 達成以後に「C 型肝炎である」と誤認された経験の有無とその症例を調査した（多施設共同研究）。

C. 研究結果

①背景因子を揃えて SVR 前 HCC の既往の有無で SVR 後の生存率を比較すると、SVR 後生存率は HCC 既往例では非既往例に比して著明に低下していた（図 1）。一方肝硬変の有無では、SVR 後の生存率に有意差はみられなかった（図 2）。

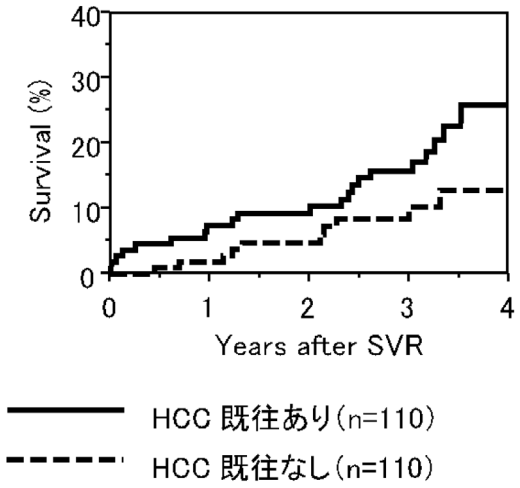


図 1

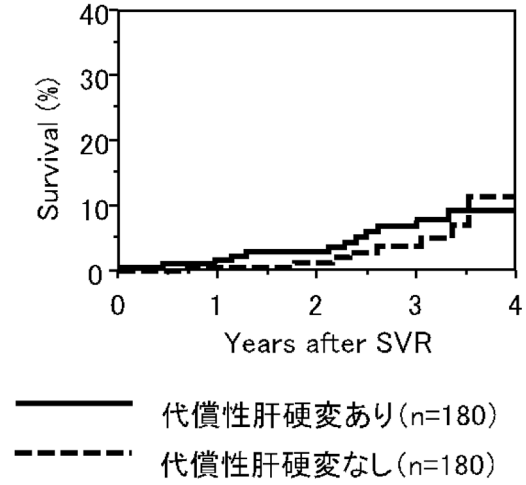
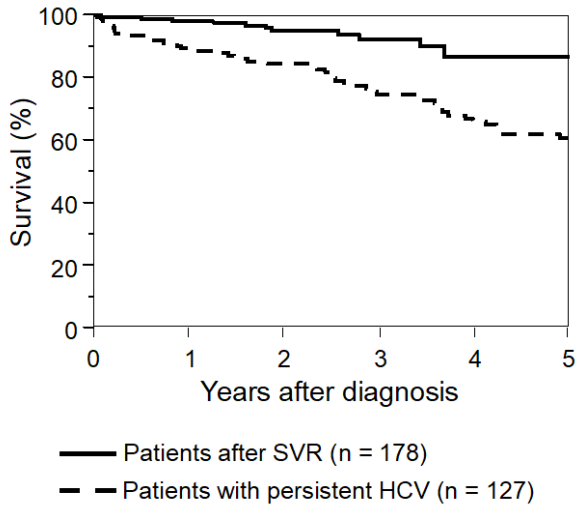


図 2

②ともにサーベイランス下で発見された SVR 後に初発した HCC178 例を HCV 持続感染中に発生した HCC127 例と比較すると、SVR 後 HCC の方がやや早期に診断されており、背景肝の肝機能が良好であった（表 1）。HCC 診断後の生存率は SVR 後 HCC が有意に高く（図 3）、これは HCC の進行度や肝機能を揃えても同様であった（図 4）。一方で根治治療後の再発率には両群間で差は見られなかったが（図 5）、再発時の肝機能は HCV 持続 HCC 症例では悪化しているのに対し SVR-HCC 症例では改善しており、再発後の生存率は SVR 症例で有意に高かった（図 6）。HCC 発生・治療後の残存肝機能の維持・改善が SVR-HCC 症例の声明予後の改善に大きく寄与していると考えられた。

	HCC after SVR (n = 178)	Control (n = 127)	p value
Age (years, median)	72 (66, 78)	74 (69, 79)	0.0555
Gender (male/female)	120 (67.4) / 58 (32.6)	81 (63.8) / 46 (36.2)	0.5412
HBsAg (negative/positive)	173 (97.2) / 5 (2.8)	123 (96.9) / 4 (3.2)	1.0000
Habitual alcohol intake (no/yes)	126 (70.8) / 52 (29.2)	97 (76.4) / 30 (23.6)	0.2970
Diabetes (no/yes)	122 (68.5) / 56 (31.5)	91 (71.7) / 36 (28.4)	0.6134
ALBI score	-2.818 (-3.063, -2.546)	-2.574 (-2.870, -2.256)	<0.0001
Maximal tumor size (cm)	1.6 (1.2, 2.0)	1.9 (1.4, 2.6)	0.0002
Number of tumors (single/multiple)	158 (88.8) / 20 (11.2)	94 (74.0) / 33 (26.0)	0.0008
Portal vein invasion (no/yes)	171 (96.1) / 7 (3.9)	126 (99.2) / 1 (0.8)	0.1546
Extrahepatic metastasis (no/yes)	178 (100) / 0	127 (100) / 0	1.0000
AFP (ng/mL)	6.3 (4.0, 15.3)	17.5 (5.3, 69.1)	<0.0001
AFP-L3 (%)	0.5 (0.5, 5.5)	5.3 (0.5, 9.1)	<0.0001
DCP (mAU/mL)	23 (18, 40)	32 (17, 76)	0.0630
Treatment (curative/non-curative)	148 (83.2) / 30 (16.9)	103 (81.1) / 24 (18.9)	0.6512

表 1



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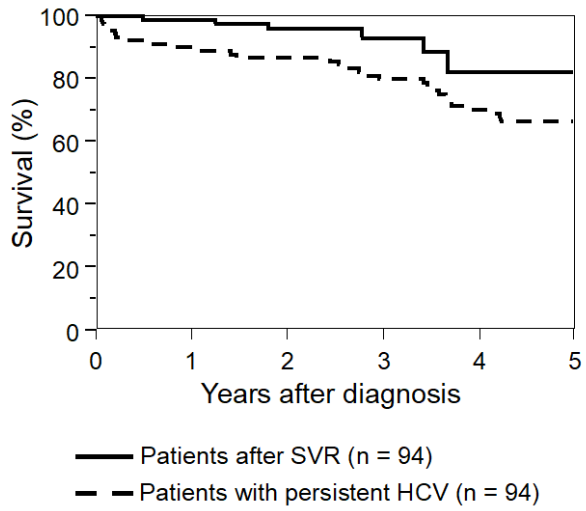

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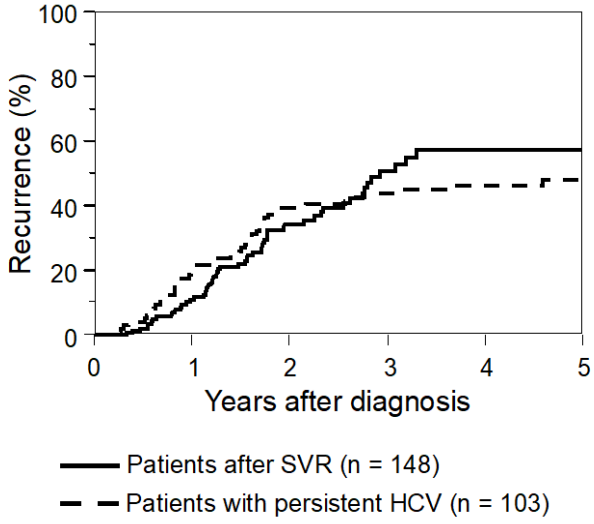

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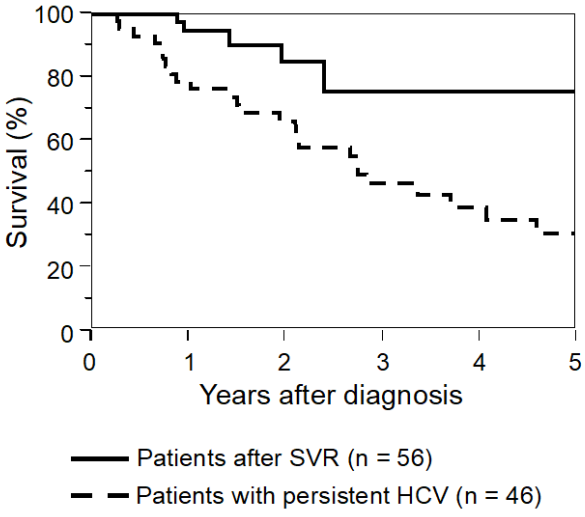
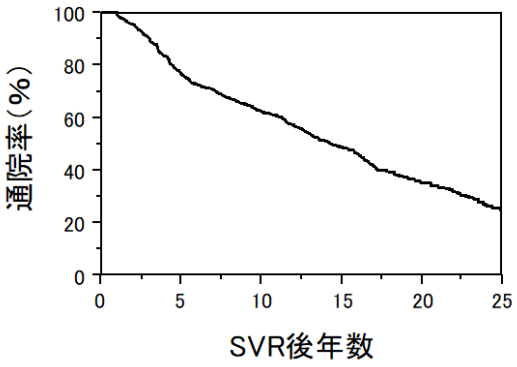


図 6

③大垣市民病院の SVR 例における SVR 後の外来通院継続率は、5 年で 76.6%・10 年で 62.4%・15 年で 48.8%・20 年で 35.3%であった（図 7）。これを年齢別にみると、高齢者で継続率が低い傾向にあったが著名な差は認められなかった。また SVR 前の肝線維化で比較すると、通院継続率は肝線維化の重度であった症例と軽度であった症例で差はなく、HCC 発生のリスクが高いとされる線維化進行例でも軽度線維化例と同程度に drop out していることがわかった（図 8）。一方、治療法別にみると、インターフェロン（IFN）治療で SVR を達成した症例に対して経口 HCV 薬（DAA）で SVR を達成した症例において明らかに通院継続率が低く（図 9）、drop out 率が高く、注意が必要であると考えられた。また genotype 別に通院継続率を見ると、genotype 2b 型に感染していた症例で有意に通院継続率が低かった（図 10）。一方、大垣市民病院で SVR を達成した HCC 既往のない 1329 例において、SVR 確定後に血中 HCV RNA をのべ 23187 回測定したが、HCV の再陽転化を認めた症例は皆無であった（表 2）。



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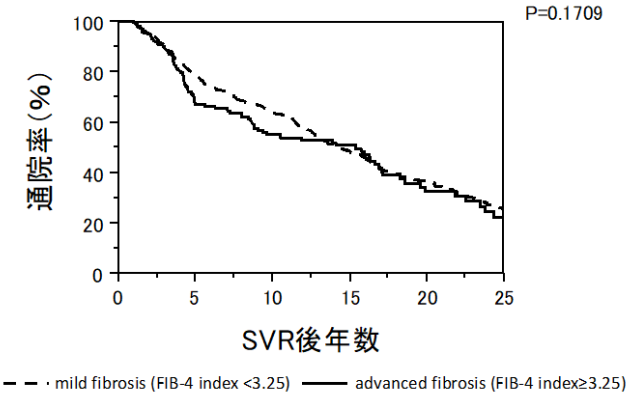

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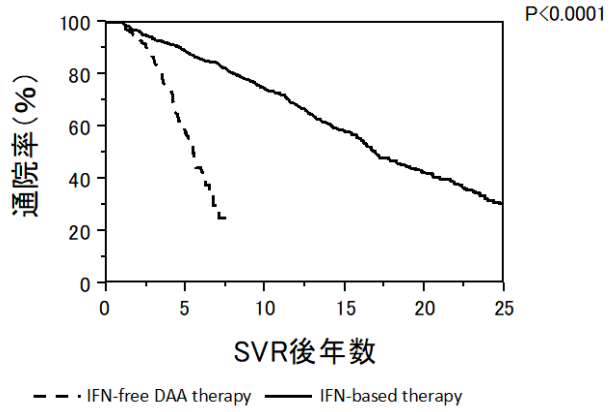

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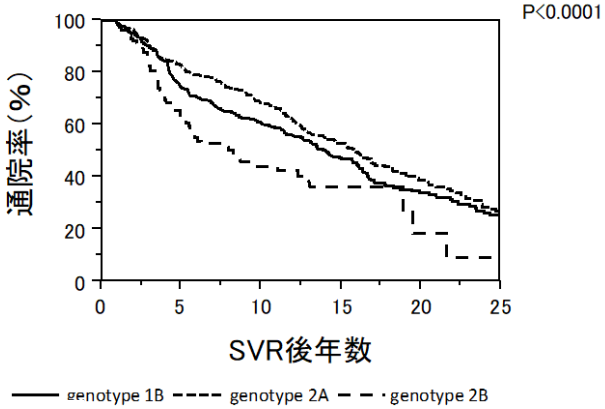

図10　HCV genotype別のSVR後通院継続率

	IFN-based therapy (N = 720)	IFN-free therapy (N = 609)
Age (years)*	55.8 (46.1–62.4)	69.9 (62.3–81.1)
Gender (male/ female)	405 (56.3) / 315 (43.8)	257 (42.2)/ 352 (57.8)
HIV coinfection	0	0
Drug user	0	0
Duration after SVR		
≤ 5 years	96 (13.3)	494 (81.1)
5< and ≤ 10 years	190 (26.4)	115 (18.9)
10< and ≤ 15 years	208 (28.9)	0
15< and ≤ 20 years	108 (15.0)	0
20< and ≤ 25 years	52 (7.2)	0
25< years	66 (9.2)	0
Number of visits	24.3 (15.0–33.2)	8.3 (6.9–9.6)
Patients with current visit	341 (47.4)	407 (66.8)
Positive HCV RNA after SVR	0	0

*SVR時の年齢

表 2

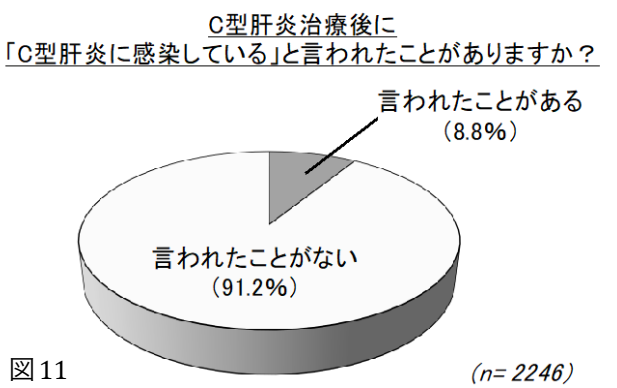

図11

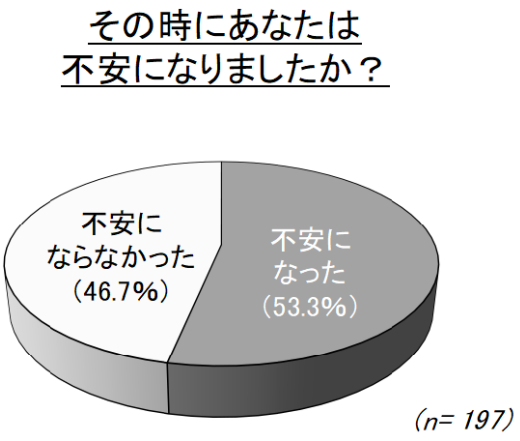

図12

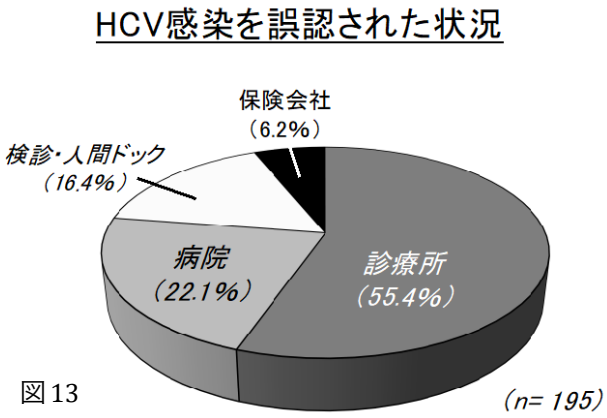

図13

④SVR 後に HCV 感染誤認についてのアンケートに同意された 2246 例を調査したところ、197 例（8.8%）で HCV 抗体陽性を根拠として HCV 感染していると誤認されていた（図 11）。このうち 105 例（53.3%）で指摘された際に自分の C 型肝炎ウイルス感染の治癒について自信をなくし不安を感じていた（図 12）。誤認された状況は診療所が 55.3%と最も多く、総合病院 22.3%、検診 16.2%の順であった（図 13）。

D. 考察

C 型肝炎 SVR 症例の SVR 後の転帰はまだまだ不明な部分が多く、今後順次明らかにしていく必要がある。今回の検討では、SVR 前に生じてしまった HCC の既往は根治治療であっても SVR 症例の生命予後を大きく損なうことが示され、HCV 感染症に対する抗ウイルス療法は HCC 発生前に行うことが重要であることを時差した。一方で肝硬変は代償期であれば、SVR によりある程度克服できる可能性が示唆された。

次に、SVR 後に発生した HCC は HCV 持続感染時に発生した HCC に比べて診断後の予後はよく、SVR 後も HCC 発生の可能性を念頭にサーベイランスを継続していくことの重要性が示唆された。

SVR 後通院継続症例においては血中 HCV が再陽転化していた症例は 1 例もなく、わが国においては、少なくとも SVR 後 drop out していない症例においては HCV の再感染はないと考えられた。一方で SVR 後 HCC サーベイランスのための定期通院率は年余により低下していた。とりわけ drop out の傾向が強かった genotype 2b 感染者はわが国において比較的若年者に多く、医療や輸血以外の感染経路の可能性が高い症例が多いと考えられている。これら症例の drop out 率が高いことは SVR 後の HCV 再感染のリスクも含め十分な留意が必要であると考えられた。

最後に、SVR・HCV 排除後にもかかわらず一般の日常臨床で HCV 感染例と誤認された経験が 10％弱の SVR 症例に見られ、昨今の極めて高い抗 HCV 療法の効果・SVR 例の増加につき今後も肝臓専門医が広く敷衍していく必要が示唆された。

E. 結論

DAA 治療により SVR 症例は飛躍的に増えたが、その経過・転帰についてはまだ十分な知見が得られていない。今後の HCC 撲滅、HCV 感染症撲滅を見据えて、さらに研究が必要と考えられる。

F. 研究発表

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